Evidence and methodology in clinical pain trials with special focus on ketamine.

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To all our pain patients - towards better clinical trials, better evidence and better pain treatments…

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Introduction

"Good evidence comes from good systematic reviews of good clinical trials"[1]

The number of scientific publications concerning pain treatment is steadily accumulating. At the same time, it is becoming increasingly difficult for both researchers and clinicians to cover the wide spectre of literature, and to understand the implication of the findings of individual trials. Systematic reviews are designed to find the best possible evidence for a specific treatment. A systematic review is however reliant on the quality and validity of the individual trials it includes and on the methods it uses. In order to get good evidence we need good quality randomised, controlled trials. Investigating the complex, subjective phenomenon of pain in the context of a controlled clinical trial is potentially difficult and good trial methodology a challenge.

Abstract

Aims

To establish the evidence base for the use of the NMDA receptor antagonist ketamine in the treatment of acute postoperative pain and cancer pain, and in doing so, to assess the methodology used in acute pain and cancer pain trials.

Methods

In paper I a clinical model was developed and tested. Paper II is a quantitative and qualitative Cochrane systematic review on perioperative ketamine for acute postoperative pain. Paper III is a qualitative Cochrane systematic review on ketamine as adjuvant to opioid for cancer pain. Paper IV is a qualitative systematic review of the methodology used in clinical trials of oral opioids for cancer pain.

Results

The model developed in Paper I was tested and found to be sensitive. Thirty-seven randomised, controlled trials (RCTs) were included in paper II. The meta-analysis found that perioperative ketamine reduced 24 hr PCA morphine consumption and reduced PONV. In paper III, four RCT's concerning ketamine as adjuvant to opioid for cancer pain were identified. Two were excluded due to flawed methodology. Both trials found that ketamine improved morphine analgesia. Meta-analysis was not appropriate. Thirty- four RCT's were included in paper IV. Significant limitations in the trial methodology were identified.

Conclusions

There is level 1 (strong) evidence that perioperative ketamine reduces 24 hr PCA morphine consumption, and post-operative nausea and vomiting. Adverse effects were mild or absent.

There is currently insufficient evidence to permit conclusions regarding the benefits and harms of ketamine as adjuvant to opioid for cancer pain. Randomised, controlled trials are needed. Clinical pain trials require rigorous methodology if they are to produce reliable results. Recommendations for future analgesic trials in acute and cancer pain are made.

List of publications

This thesis is based on the following original papers referred to in the text by Roman numerals:

I. Bell RF, Sivertsen Å, Mowinckel P, Vindenes H. A bilateral clinical model for the study of acute and chronic pain after breast-reduction surgery. ***Acta Anaesthesiol Scand 2001; 45 (5):576-582***.

II. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. ***The Cochrane Database of Systematic Reviews 2006, Issue 1. Art.No.:CD004603. DOI: 10.1002/14651858. CD004603.pub2.***

Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain. A quantitative and qualitative systematic review (Cochrane review). ***Acta Anaesthesiol Scand 2005;49(10):1405-1428***

III. Bell R, Eccleston C, Kalso E. Ketamine as adjuvant to opioids for cancer pain. ***The Cochrane Database of systematic reviews 2003, Issue 1. Art No.:CD003351. DOI:10.1002/14651858. CD003351***

Bell RF, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. A qualitative systematic review. J Pain Symptom Manage 2003;26;3:867-875

IV. Bell RF, Wisløff T, Eccleston C, Kalso C. Controlled clinical trials in cancer pain. How controlled should they be? A qualitative systematic review. ***Br J Cancer 2006; 94:1559-1567***

Abbreviations

5-HT	Serotonin
ACC	Anterior cingulate cortex
AHRQ	Agency for Healthcare Quality and Research
AMPA	α-amino-3-hydroxy-5-methyl-4-isaxazole propionic acid
AUC	Area under the curve
Bc	Brachium conjunctivum
BDI	Beck Depression Inventory
cc	Corpus callosum
Ce	Central nucleus of the amygdala
CCK	Cholecystokinin
CGMP	Cyclic guanosine monophosphate
CGRP	Calcitonin gene related peptide
CNS	Central nervous system
CONSORT	Consolidation of Standards for Reporting Trials
DRG	Dorsal root ganglion
EBM	Evidence based medicine
GABA	γ-aminobutyric acid
Hip	Hippocampus
IASP	International Association for the Study of Pain

Ic	Internal capsule
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
IV	Intravenous
LC	Locus coeruleus
LTP	Long term potentiation
Mg^{+}	Magnesium
MgluR	Metabotropic glutamate receptor
NHH	Number Needed to Harm
NK	Neurokinin
NNT	Number Needed to Treat
NMDA	N-Methyl-D-Aspartate
NRM	Nucleus raphe magnus
NSAIDs	Non-Steroidal Anti- Inflammatory Drugs
OPVS	Oxford Pain Validity Scale
OR	Odds ratio
ORL1	Opioid receptor-like receptor
PAG	Periaqueductal Grey
Pb	Parabrachial area
PCA	Patient Controlled Analgesia
PCP	Phencyclidine
PET	Positron Emission Tomography

Po	Posterior group of thalamic nuclei
POMS	Profile of Moods States
Py	Pyramidal tract
QST	Quantitative Sensory Testing
QUOROM	Quality of Report of Meta-analyses
RCT	Randomised Controlled Trial
RVM	Rostroventromedial medulla
TOTPAR	Total Pain Relief
V	Ventricle
VASpi	Visual Analogue Scale for pain intensity
VMH	Ventral medial nucleus of the hypothalamus
VPL	Ventral posterolateral nucleus of the thalamus
VPM	Ventral posteromedial nucleus of the thalamus
WHO	World Health Organization
WMA	World Medical Association
WMD	Weighted mean difference

Contents

1. Background

1.1 Pain

The International Association for the Study of Pain (IASP) defines pain as:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Much thought has gone into this definition, which attempts to capture the many different aspects of pain. Pain may be present with, or without tissue damage. The ability to feel pain is critical, in order to protect the body from injury. However, pain may change character and become persistent and refractory to treatment. Pain is subjective, and the perception of pain is influenced by the context in which the pain arises [2-4 5]. This makes pain difficult to measure and may also make it difficult to treat.

1.1.1 Anatomy and neurophysiology

"Pain is not a passive consequence of the transfer of a defined peripheral input to a pain center in the cortex, but an active process generated partly in the periphery and partly within the CNS by multiple plastic changes that together determine the gain of the system." [6]

Between the delivery of a painful stimulus and the subjective experience of pain is a series of complex events involving four distinct processes: *Transduction, transmission, modulation* and finally *perception*, when the pain signal is relayed to the brain resulting in the multidimensional experience of pain which involves sensory-discriminative, affective-motivational and cognitive components[7].

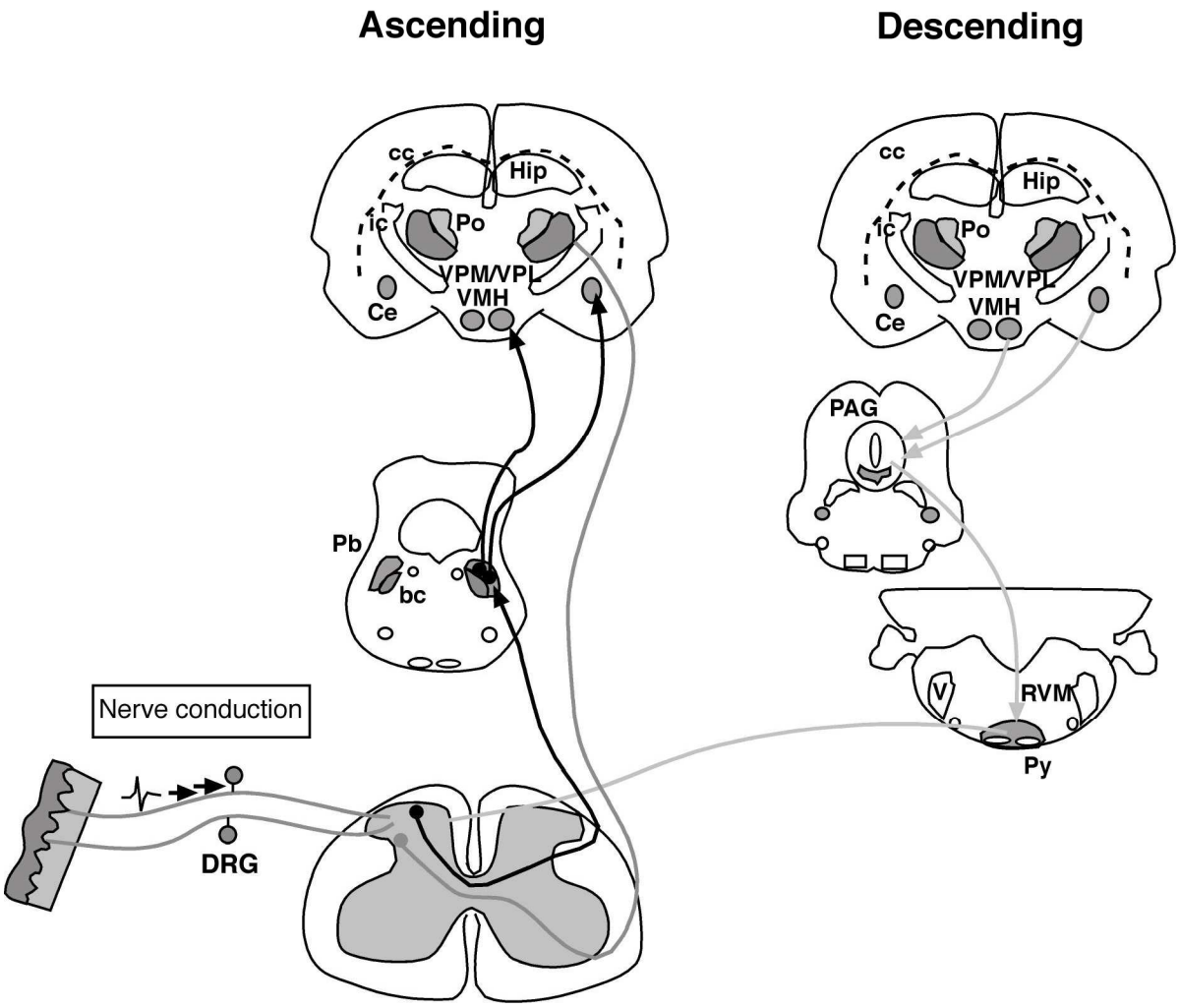

Figure 1. Pain pathways (adapted from ANZCA[8])

PAG: periaqueductal grey
cc: corpus callosum
Ce: central nucleus of the amygdala
Hip: hippocampus
ic: internal capsule
LC: locus coeruleus
DRG: dorsal root ganglion
RVM: rostroventromedial medulla
Pb: parabrachial area
Po: posterior group of thalamic nuclei
Py: pyramidal tract
V: ventricle
VMH: ventral medial nucleus of the hypothalamus
VPL: ventral posterolateral nucleus of the thalamus

VPM: ventral posteromedial nucleus of the thalamus
Bc: brachium conjunctivum

Activation of the pain system: transduction and transmission

Transduction

Painful stimuli are registered by specific pain receptors (nociceptors), which are the free nerve endings of peripheral sensory neurons (Aδ and C fibres). The nociceptors transform pain information into electrophysiological activity, depolarising currents. The central termination of these fibres is in the dorsal horn of the spinal cord where they synapse with central nervous system (CNS) neurones.

Transmission

If sufficient depolarising current, transduction is followed by initiation of action potentials and relay of coded information to the CNS. Initially impulses are conducted in primary afferent neurons to the dorsal horn of the spinal cord, from where secondary sensory afferent neurones ascend to the brainstem and thalamus. Thereafter, reciprocal connections are made between the thalamus and higher areas of the brain concerned with the perception of, and affective response to pain. Acute noxious inputs are mediated by glutamate acting on the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor. At the same time, inhibitory neurones releasing mainly glycine and γ-aminobutyric acid (GABA) are activated.

Activation-dependent plasticity

The nervous system changes its structure and function in response to the input it receives. In the case of activation of nociceptive pathways, there is a progressive increase in the response

to stimulation. Persistent neuronal activity leads to changes in neural function and results in the amplification of pain. This ”plasticity” is evident at all levels, from the periphery to the cortex.

Activation –dependent plasticity in dorsal horn neurones

Electrophysiological experiments have demonstrated a phenomenon entitled ”*wind-up*”, which is an example of activation-dependent plasticity in dorsal horn neurones. Intense or sustained nociceptive input results in the co-release of neuromodulators, as well as glutamate [6], the process being augmented by activation of the N-methyl-D-aspartate (NMDA) receptor. The net effect is that repeated C fibre stimulation results in a wind-up of action potential discharge and postsynaptic hyperactivity of dorsal horn nociceptive neurones. Wind-up may be inhibited by NMDA receptor antagonists such as ketamine [9]. *Long term potentiation* (LTP) is a similar, but more persistent effect than wind-up, which can be evoked in a subpopulation of dorsal horn neurones by specific short- duration, high-frequency stimulation.

Modulation: peripheral and central sensitisation

The pain signal is potentially subject to modulation at a number of sites, both in the dorsal horn, and through supraspinal or descending control. Nociception does not always result in pain perception, and equally, pain may be perceived in the absence of nociception. Modulation of nociception occurs at all levels of the neuraxis.

Peripheral sensitisation

Peripheral nociceptors can be sensitised by injury, decreasing threshold and increasing response to noxious stimuli. The sensitising agents include inflammatory mediators such as

prostaglandins, bradykinin, serotonin, leucotrienes and Substance P, and neurotrophic factors released during tissue damage or by inflammatory cells. Primary afferents which are not usually stimulated by noxious and non-noxious stimuli may become activated. This process of sensitisation results in *hyperalgesia* (an increased response to a stimulus which is normally painful).

Central sensitisation

Activity-dependent enhancement of nociceptive transmission is common at excitatory synapses throughout the CNS, and increased activity of sensitised nociceptive primary afferent neurones results in increased excitability of spinal cord neurones. This modulation includes reduction in activation threshold, increased responsiveness, and expansion of the receptive field, resulting in enhancement of nociceptive input to higher centres. The increased excitability either outlasts the initiating input or requires low-level peripheral drive to maintain it [6]. This process is termed *central sensitisation* and is responsible for *allodynia* (pain due to a stimulus which does not normally provoke pain) in the injured area.and the spread of hypersensitivity to areas beyond the site of injury. Central sensitisation is a major component of inflammatory and neuropathic pain.

Table 1. Some of the important neurotransmitters in the dorsal horn mediating/ modulating pain (modified from Beaulieu and Rice [7])

Neurotransmitter	Receptor	Effect on nociception
Nonpeptides		
Monoamines:		
Noradrenaline	A_2-adrenergic	Inhibitory
Serotonin (5-HT)	5-HT_1, (5-HT_2), (5-HT_3)	Inhibitory
Amino acids:		
GABA	$GABA_A$, $GABA_B$	Inhibitory
Glycine		Inhibitory
Glutamate	NMDA, AMPA, kainate, mGluR	Excitatory
Aspartate	NMDA, AMPA, kainate, mGluR	Excitatory
Acetylcholine	Muscarinic	Inhibitory
Peptides:		
Opioids:		
Enkephalins	Δ(DOP)	Inhibitory
B-Endorphins	Δ (DOP), μ (MOP)	Inhibitory
Dynorphin	K (KOP)	Excitatory
Non-opioids:		
Substance P	NK1	Excitatory
CGRP	CGRP	Excitatory
CCK	CCK_B	Excitatory or inhibitory dependent on site
Galanin	GAL	Excitatory or inhibitory dependent on site
Somatostatin	Sst	Inhibitory
Neuropeptide Y	Y_1, (Y_2)	Inhibitory
Neurotensin	NTS_1	Inhibitory
Bradykinin	B_2, (B_1)	Excitatory
Other:		
Adenosine	A_1	Inhibitory
Purines	$P2X_3$	Excitatory
Cytokines	Interleukins, TNF	Excitatory and inhibitory
Capsaicin	VR1	Excitatory
Cannabinoids	CB_1	Inhibitory

GABA: γ-aminobutyric acid
CGRP: Calcitonin gene related peptide
NMDA: N-methyl-D-aspartate
AMPA: α-amino-3-hydroxy-5-methyl-4-isaxazole propionic acid
MGluR: metabotropic glutamate receptor
CGMP: cyclic guanosine monophosphate
NK: neurokinin
CCK: cholecystokinin

The opioid and NMDA receptor systems, which show a close distribution pattern in the CNS, appear to be the two most important systems in modulating nociception, having respectively antinociceptive and pronociceptive actions.

Excitatory systems: the role of the NMDA receptor

Activity- dependent augmentation of nociceptive transmission may be divided into N-methyl-D-aspartate (NMDA) receptor-dependent and NMDA receptor- independent types. NMDA is not an endogenous substance, but a research tool which has been used to identify a receptor active in glutaminergic transmission. The amino acids *glutamate* and *aspartate* are the major neurotransmitters in excitatory transmission at the spinal level. They are stored in the terminals of primary afferent nociceptors and are released in response to nociceptive activity. Glutamate is the major excitatory neurotransmitter and is utilized by 40% of all synapses[10]. There are three main receptors for glutamate on nociceptive C fibre afferents: the α-amino-3-hydroxy-5-methyl-4-isaxazole propionic acid (AMPA), the metabotropic and the NMDA receptors.

The NMDA receptor

NMDA receptors are located in the brain, spinal cord and on peripheral nociceptors and are concentrated at postsynaptic sites, although some appear to be pre-synaptic[11]. The receptor is an ionotropic (ligand gated ion channel) receptor composed of at least two families of subunits, the NR1 and NR2 subfamilies. The channel is permeable to Ca^{++} and to a lesser degree, to Na^{+} and K^{+}. Glutamate binds to the NR2 subunit, while the NR1 subunit binds glycine, which is required as a co-agonist for receptor activation [12] (figure 2).The receptor is inhibited by Mg^{+} in a voltage-dependent manner. The NR1 and NR2 subunits occur in heterogenous forms, the NR2B subunit being implicated in pain perception and currently

being targeted for the development of new analgesics[13]. Excessive release of glutamate, or excessive stimulation of NMDA receptors within the nervous system, can lead to excitotoxic injury or cell death [12]. NMDA receptor antagonists, including ketamine, have been shown in animal models of ischemic neuronal injury to have a neuroprotective effect[14 15 16]. However, the clinical benefits of this have not been demonstrated.

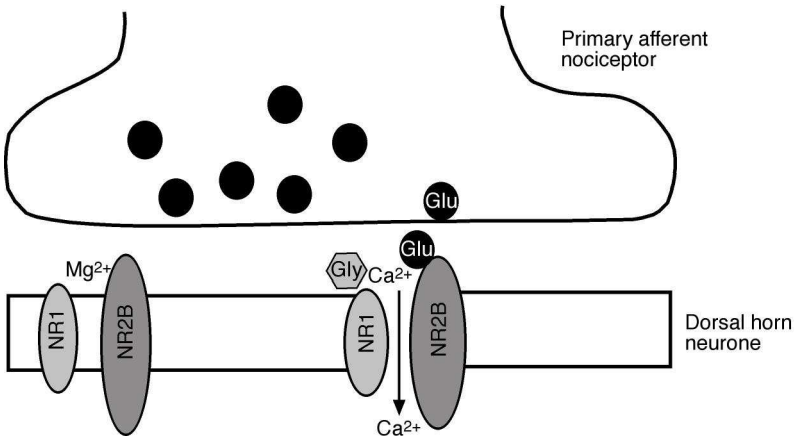

Figure 2: Schematic representation of the NMDA receptor showing NR1 and NR2B subunits. Closed ion channel on the left, and open on the right: (modified from Loftis et al.[13])
Gly: glycine
Glu: glutamate

The NMDA receptor and hyperalgesic pain

Acute noxious inputs are transmitted by the AMPA receptor. In contrast, the NMDA receptor does not appear to be involved in baseline transmission of pain signals, but in the modulation (amplification) of pain, being implicated both in central and peripheral sensitisation [17]. The channel of the NMDA receptor is usually blocked by magnesium and it is thought that in response to a continuing painful stimulus, the magnesium block of NMDA channels is removed and the NMDA receptor activated (fig.2).

Both inflammatory pain and pain due to nervous tissue lesion are characterised by hypersensitivity at the site of injury and in the adjacent tissue. Inflammatory pain hypersensitivity usually returns to normal in conjunction with healing, while neuropathic pain persists long after healing, and is an expression of pathological enhanced activity in the nervous system. NMDA receptor antagonists such as ketamine and dextromethorphan have been shown to prevent or block enhanced, or hyperalgesic, pain states induced by tissue damage, inflammation, nerve damage and ischaemia[9]. The upregulation and activation of peripheral NMDA receptors contributes to the sensory changes (mechanical hyperalgesia and heat sensitisation) which usually accompany chronic inflammation[17]. Animal studies have demonstrated that the expression of peripheral NMDA receptors increases under conditions of inflammation[18 17], and that peripheral NMDA receptors contribute to nociception in normal skin and maintain peripheral sensitisation in chronically inflamed skin[17].

The NMDA receptor and other modulatory functions

The NMDA receptor is also implicated in other modulating functions such as learning and memory processing[13]. Excitatory glutamatergic neurotransmission is believed to be involved in the pathophysiology of depression: antidepressant treatments, including tricyclic antidepressants induce changes in NMDA receptor-binding characteristics, and modulate long term potentiation (LTP)[19]. Selective NMDA receptor antagonists have been shown to have antidepressant- like effects in animal behavioural models[20] and case studies reporting improvement of major depression with ketamine infusions have recently been reported[21]. A deficit in NMDA transmission has been implicated in the pathophysiology of schizophrenia[10].

NMDA receptor- independent mechanisms of pain facilitation

NMDA receptor-independent mechanisms for facilitating pain transmission include certain dorsal horn AMPA receptors which allow calcium influx producing lasting facilitation of synaptic transmission in dorsal horn neurons. In addition, activation of Aδ afferents may result in long-term depression of spinal inhibitory mechanisms, a process involving GABA/ glycinergic neurons in the substantia gelatinosa[6].

Inhibitory systems

Opioids are the major inhibitory neurotransmitters. There are four major classes of *opioid receptor*: μ, κ, δ and opioid-receptor-like (ORL1) receptors. Opioid receptors are widely distributed throughout the central nervous system, in somatic and visceral sensory neurones, spinal cord projection and interneurons, midbrain and cortex. Opioid receptors have also been identified on the peripheral endings of sensory neurones, the number of receptors increasing under conditions of inflammation or neuropathy[22]. Sympathetic neurones and immune cells can also express opioid receptors. Mu-opioid receptors dominate in the spinal cord, where they are found at the terminal zones of C-fibres, mainly in Lamina 1, and in the substantia gelatinosa. Opioid receptor agonist action inhibits the conduction of signals in nociceptive pathways in several ways, including the prevention of calcium influx at presynaptic calcium channels, which in turn inhibits the release of neurotransmitters[23].

Opioid receptors are believed to be reciprocally modulated by the NMDA receptor[12]. The NMDA receptor appears to be involved in the mechanism of opioid tolerance, and the blockade and reversal of opioid tolerance by NMDA receptor antagonists has repeatedly been demonstrated in animal models[24 25 26]. One hypothesis of opioid tolerance is that stimulation of opioid receptors triggers activation of antiopioid systems, that in turn produce hyperalgesia, thus reducing the net effect of the opioid[27]. Opioids have been shown to have

excitatory (pronociceptive) activity in animal models[28 29], and numerous clinical reports confirm that chronic opioid administration may result in hyperalgesia.

In addition, descending axons of serotonergic and noradrenergic neurones interact with primary afferent neurones in the dorsal horn to modulate the transmission of nociceptive information. This descending control of pain occurs primarily through two pathways originating in the midbrain (periaqueductal grey (PAG), and locus coeruleus (LC)), and the medulla (nucleus raphe magnus (NRM)) (fig.1). The main neurotransmitters involved in descending pain control are serotonin (5-HT), noradrenaline, dopamine and opioid peptides.

Excitatory and inhibitory system interaction

It has long been known that supraspinal centres modulate spinal nociceptive transmission via an endogenous opioid descending inhibitory system. More recently, it has been shown in animal studies that descending control is bi-directional via inhibitory and facilitatory systems, and that it is likely that these opposing systems are activated simultaneously by peripheral nociceptive afferent activity in conditions of acute nociception. In the case of persistent noxious input, it has been suggested that NMDA-receptor dependent neuroplastic changes could occur in the rostroventromedial medulla (RVM), which is an important midbrain relay station for descending modulation[30]. Such changes could lead to sustained facilitation of descending facilitatory pathways, a possible mechanism underlying some states of inflammatory and neuropathic pain[30]. In addition, the anterior cingulate cortex (ACC) which is involved in the processing of sensory and emotional components of pain, is widely connected to regions of the descending modulatory system. Recent animal studies indicate that activation of the ACC may also facilitate spinal nociception, and that NMDA receptors in the ACC may be involved in descending facilitation[31].

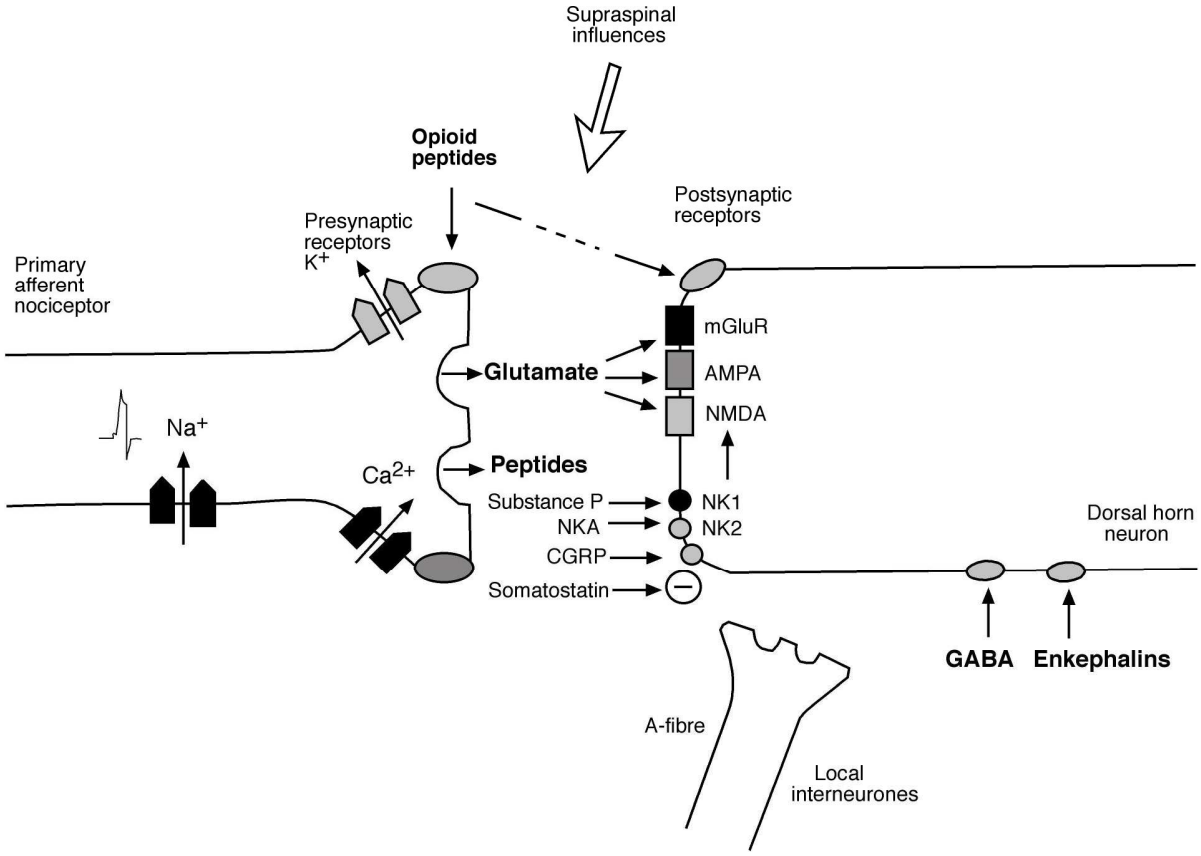

Figure 3. A schematic diagram of the synapse between C fibre and dorsal horn neurone illustrating release of neurotransmitters and neuropeptides and interactions between excitatory and inhibitory systems (modified from Beaulieu and Rice[7])

MgluR: metabotropic glutamate receptor
AMPA: α-amino-3-hydroxy-5-methyl-4-isaxazole propionic acid receptor
NMDA: N-Methyl-D-aspartate receptor
NKA: Neurokinin A
CGRP: Calcitonin gene-related peptide
NK1: Neurokinin 1 receptor
NK2: Neurokinin 2 receptor
GABA: γ-aminobutyric acid

1.1.2 Clinical pain

In clinical practice, it is usual to distinguish between acute pain, chronic non-cancer pain and pain due to cancer. These types of pain respond differently to treatment and are handled

differently. *Nociceptive pain* arises in conjunction with stimulation of specific pain receptors (nociceptors). *Neuropathic pain* is initiated or caused by a primary lesion or dysfunction in the nervous system[32]. Neuropathic pain may be characterised by hyperalgesia, and/ or other signs of pathology such as allodynia.

Acute pain

Acute pain is defined as *pain of recent onset and probable limited duration*[33] and arises in connection with tissue injury, involving the stimulation of nociceptors. Acute pain involves an inflammatory response and may also have a neuropathic pain component. Acute pain may progress to chronic pain, and there is a wealth of literature documenting chronic pain after surgery. For example, Tasmuth et al[34] found that one third to half of patients suffered from pain or paresthesia after modified radical mastectomy with axillary dissection or breast resection with axillary dissection. Kalso et al[35] found that 28% of patients reported persistent post-sternotomy pain after coronary bypass surgery. Cunningham et al[36] found that at 2 years, 54% of patients had pain after hernia repair. In addition, a number of studies have identified pre-or postoperative pain intensity as a risk factor for chronic pain after surgery[37]. There is some evidence that specific early analgesic interventions may reduce the incidence of chronic pain after surgery[8 38]. Other factors such as genetic differences [39] and sex and gender[40] may influence pain and the efficacy of pain treatment.

Acute pain generally responds well to medical interventions, such as drugs (opioids, NSAIDs) and anaesthesiological techniques such as spinal, epidural and regional nerve blocks. In cases of refractory acute pain, it is important to consider the patient's history, psychosocial situation and the acute pain setting, in order to identify factors which may be

exacerbating the pain. Opioid- dependent patients may for example experience severe pain after surgery because the post-operative opioid dose is too low compared to the baseline opioid requirement[41]. Psychological factors such as anxiety and catastrophising can contribute to the intensity of pain[42].

Cancer pain

Pain due to malignancy may be both acute and chronic. Cancer patients commonly experience several types of pain concurrently. Tumour expansion can cause pressure on surrounding organs, while tumour infiltration in nerve plexi and bone, and damage of nerve tissue can cause neuropathic pain. Metastatic spread of cancer to bone is reported to be one of the most common causes of cancer pain[43], and may cause pain both at rest and on movement. Cancer patients may experience muscular pain due to rapid weight loss. They are potentially subject to painful adverse effects of treatment, such as joint pain following chemotherapy, painful mucositis, and acute and/ or persistent neuropathic pain following radio- or chemotherapy. Cancer patients are often exposed to surgical interventions and experience acute, and in some cases chronic post-operative pain.

Table 2. Cancer pain

Examples of cancer pain subtypes	Possible pain mechanisms
Tumour related	Sensitisation of peripheral nociceptive primary afferents (inflammation associated factors, tumour factors,eg.endothelin and prostaglandins, tumour- induced acidosis); invasion of mechanically sensitive tissues (e.g visceral pain); entrapment and nerve injury; central sensitisation.
Metastatic bone pain	Tumour-induced release of protons and acidosis; injury or infiltration of sensory neurones that innervate the bone marrow; peripheral sensitisation of nociceptors[44]; osteolysis, pathological fracture, microfractures.
Metastatic soft tissue pain	Peripheral sensitisation due to inflammation. Hyperalgesia due to central sensitisation.
Inflammatory (e.g. mucositis)	Peripheral sensitisation due to inflammation. Hyperalgesia due to central sensitisation.
Neuropathy	Nervous tissue compression or lesion→central sensitisation. Disruption of tubulin function by chemotherapeutic agents, with release of cytokines, resulting in degeneration of sensory neurones and sensitisation of primary nociceptive afferents[44].
Muscle pain	Tumour factors; central sensitisation; bone metastases causing muscle spasm; muscle hypercatabolism; immobilisation; increased muscular tension.
Acute postoperative pain	Acute nociception; peripheral sensitisation; nerve damage; (central sensitisation)
Chronic postoperative pain	Central sensitisation; nerve damage; (peripheral sensitisation)

The World Health Organisation (WHO) three-step ladder for cancer pain relief [45] advises that mild cancer pain should be treated with non-opioid analgesics (paracetamol and/ or NSAIDs), moderate pain with the addition of weaker opioids, and strong pain with the substitution of stronger for weaker opioid. The utility of the second step on the ladder has

been challenged, with suggestions to replace step-two opioids with stronger opioid. Morphine is the"gold standard" opioid for cancer pain.

Neuropathic pain

Neuropathic pain is difficult to treat with opioids alone and usually requires adjuvant drugs such as tricyclic antidepressants (eg. amitriptyline), or anticonvulsants (eg.gabapentin or pregabalin). Refractory neuropathic pain requires other measures, such as adjuvant treatment with an NMDA receptor-antagonist, or anaesthesiological techniques such as spinally administered local anaesthetic as an adjuvant to opioid.

Intermittent or breakthrough pain

Breakthrough, or incident pain is common in cancer patients, with bone pain, local tumour invasion in soft tissue, and brachial plexopathy most frequently reported[46]. Breakthrough pain usually occurs at the site of the background pain and the duration may vary from minutes to hours[47]. Intense, short-lasting pain episodes and movement- related pain are particularly difficult to treat effectively with analgesics. Normal-release oral opioid or oral transmucosal fentanyl citrate are at present the most common pharmacological treatment options for breakthrough pain.

The potential complexity of the cancer patient's pain syndrome (table 2) underscores the importance of repeated clinical assessment and pain diagnosis, together with an individual treatment plan.

Chronic non-cancer pain

The IASP defines chronic pain as pain without apparent biological value that has persisted beyond the normal tissue healing time (usually considered to be 3 months). Chronic pain is a complex condition which may be related to tissue damage, injury to the nervous system, affective state and interactions of the individual with the environment. Chronic pain often requires a multidisciplinary approach including a comprehensive and individually tailored treatment programme which may involve pharmacological, psychological and physical interventions.

1.2 Ketamine

1.2.1 General

Ketamine is a phencyclidine (PCP) derivate, developed in the 1960's as an anaesthetic agent. Ketamine has multiple pharmacological effects and interacts with a large number of receptors and channels, including nicotinic and muscarinic acetylcholine receptors, opioid receptors, monoaminergic and voltage-sensitive calcium channels, and sodium channels. Ketamine has a direct action on the NMDA receptor, binding to the PCP binding site in the NMDA channel, thus inhibiting glutamate activation of the channel in a non-competitive manner. The analgesic effect of ketamine is thought to be due to this antagonistic effect on the NMDA receptor. This is due to the fact that both ketamine isomers have been found to have higher affinity for the NMDA receptor PCP binding site than for other sites and channels[48 49], and that ketamine analgesia appears due to a non-opioid mechanism[48 50 51].

NMDA receptor activation is believed to be central to the generation and maintenance of hyperalgesic pain[9], and NMDA receptor antagonists, such as ketamine, have been shown to inhibit hyperalgesia/ allodynia[52]. Non-competitive NMDA receptor antagonists, including ketamine, have also been shown in animal studies to attenuate the development of opioid tolerance [53]. These factors make ketamine an interesting drug for the treatment of refractory pain.

Ketamine was previously only available as a racemic mixture of the two stereoisomers, S(+) and R(-) ketamine. Both isomers and the metabolite, norketamine, have been shown in animal studies to be NMDA receptor antagonists [54]. Most clinical studies on the analgesic effects of ketamine have used racemic ketamine. More recently, the S(+) ketamine isomer has been approved for clinical use. The S(+) isomer is approximately twice as potent as the racemic mixture[55]. S(+) ketamine produces longer hypnosis than the R(-) isomer, and causes a greater rise in blood pressure and heart rate, less locomotor activity, and a shorter recovery time, but equipotent analgesia. An investigation using positron emission tomography in healthy volunteers, has shown that S(+) ketamine binds to specific areas in the brain corresponding to regions with a high density of NMDA receptors[56]. S(+) ketamine is generally thought to have a safer adverse effect profile than racemic ketamine[57], although there seems to be little clinical trial data to support this. A recent study by Lahtinen et al[58] found an eight percent incidence of psychotomimetic adverse effects in patients treated with S(+) ketamine after cardiac surgery.

1.2.2 Pharmacokinetics

Pharmacokinetically, ketamine has short distribution and elimination half-lives, the alpha-elimination phase lasts only a few minutes and the beta-elimination half-life is 2-3 hours.

Ketamine undergoes extensive hepatic metabolism by the cytochrome p450 system, primarily via N-demethylation to *norketamine*, and has been shown to have stereoselective pharmacokinetics. Both ketamine and metabolites are renally excreted.

Norketamine is also an NMDA receptor antagonist, having a 2-4 fold lesser affinity for the non-competitive site of the NMDA receptor than ketamine, and being only one third to one fifth as potent as ketamine. Norketamine has been shown to have dose-dependent antinociceptive effects[59]. Other metabolites of ketamine are mainly hydroxynorketamines which have poor lipid solubility and do not have CNS activity. Ketamine enantiomers differ in their hepatic clearance and duration of anaesthetic effect. S(+) ketamine exhibits a greater clearance and faster anaesthetic recovery compared to the racemate and a greater clearance compared to R(-) ketamine[60]. R(-)-ketamine inhibits the elimination of S(+)-ketamine[61].

The pharmacokinetics and analgesic effects of intramuscular and oral racemic ketamine in a dose of 0.5 mg kg^{-1} were examined in a group of six healthy volunteers[62] in a randomised, single-blind, placebo-controlled crossover study. Pain thresholds measured by the tourniquet test were increased at 15 min and 30 min after i.m.injection and at 30 min after oral ketamine. The plasma ketamine concentration associated with analgesia was 150 ng ml^{-1} following the i.m. dose, but only 40 ng ml^{-1} after the oral dose. Oral administration was associated with much greater concentrations of the metabolite norketamine which it was speculated may have contributed to the analgesia. This single-blind study has resulted in some confusion regarding the potency of oral ketamine and has been cited in support of a claim that oral ketamine is more potent than parenteral ketamine[63].

The same research group the following year published a randomised, double-blinded placebo controlled crossover study in healthy volunteers, investigating the pharmacokinetics of intramuscular racemic ketamine (N=6) compared to intravenous (N=5) or oral racemic ketamine (N=6)[64]. Absorption after intramuscular injection was rapid and the bioavailability was 93%. However, only 17% of an oral dose was available due to extensive first-pass metabolism. In this study, pain thresholds measured in the same tourniquet test showed marked elevation for 15-60 min after intramuscular injection, but little or no effect after the oral solution. Pain threshold elevation occurred at plasma ketamine concentrations above 160 ng/ml. In contrast to the previous study, the authors concluded that, in view of the extensive first-pass metabolism, oral administration of ketamine in a dose of 0.5 mg/kg is not satisfactory for producing analgesia.

A randomised, controlled trial investigated intranasal ketamine for breakthrough pain[65]. Plasma concentrations of ketamine were measured at two, 30 and 60 minutes after intranasal spray administration. Plasma levels were detectable by 2 minutes after administration and the observed mean concentration of ketamine was greatest at 30 minutes after administration, corresponding to the interval of greatest decrease in pain intensity scores. At the last observed time (60 minutes), mean ketamine levels had declined by approximately 20% from peak values.

In a preclinical study [66], the pharmacokinetics of ketamine and alfentanil, alone and together, in three groups of adult male rats, were determined to assess any pharmacokinetic interaction. The distribution of ketamine into the brain was increased by low, constant plasma concentrations of alfentanil. To date there is no human data on the pharmacokinetics

of ketamine co-administered with morphine. Such a study would be interesting, and may further our understanding of the apparent synergism of these two drugs.

The pharmacokinetic data on ketamine and isomers is limited. For example, a search of PubMed in April 2006 revealed no studies where intravenous S(+) ketamine was compared with oral S(+) ketamine. Since both racemic and S(+) ketamine are increasingly being used in the treatment of refractory pain, there is a need for more data.

1.2.3 Toxicology and abuse

The clinical use of ketamine is thought to be limited by psychotomimetic and other adverse effects which include hallucinations, agitation, nightmares, dizziness and nausea. At higher doses (>2 mg/kg, IV)[67] ketamine can cause delirium, impaired motor function, amnesia, anxiety, panic attacks, mania, insomnia, and high blood pressure.

NMDA receptor antagonists including ketamine, GABA receptor agonists and ethanol have all been demonstrated in studies in immature rodents to trigger widespread apoptotic neurodegeneration throughout the developing brain[68 69]. In addition, there is controversy in the literature regarding the safety of epidural and spinal administration of ketamine[70], some animal studies and isolated clinical reports having described toxic effects[71 72 73 74].

Ketamine is increasingly used as a drug of abuse in Western countries[75] and was recently re-classified as a controlled drug in the UK. Although the mortality rate is low, there are

concerns regarding the neurotoxic effects. Recreational users report flashbacks which can recur days or weeks after use[76]. Frequent abuse of ketamine has been shown to cause long-lasting memory impairment[77] and a recent PET study found altered prefrontal dopaminergic function in chronic recreational users of ketamine[78].

It was previously thought that tolerance does not develop to ketamine. However, animal studies indicate that ketamine can give rise to a dependence syndrome without physical withdrawal phenomena[79]. Reports from recreational users confirm that tolerance builds rapidly and can be very high, and that users can experience psychological dependence and craving, with little documented evidence of physiological withdrawal symptoms[80]. Recreational users usually administer ketamine intranasally, although it is also injected. A randomised controlled trial has been published investigating the use of intranasal ketamine for breakthrough pain[65]. Although intranasal ketamine may have potential for the relief of breakthrough pain in terminally ill cancer patients, it would seem prudent to exercise caution with regard to use of this rapid- acting route of administration in the treatment of chronic non-cancer pain[81].

1.2.4 The clinical use of NMDA receptor antagonists

Given the role of the NMDA receptor in central sensitisation, in opioid tolerance, and possibly in the chronification of pain, NMDA receptor antagonists are potentially interesting drugs for the treatment of refractory pain. A number of NMDA receptor antagonists including dextromethorphan, ketamine and memantine are clinically available, although it is generally believed that psychotomimetic adverse effects limit their usefulness. Memantine

has recently been approved for the treatment of dementia[12] and future possiblities for the treatment of neurological disorders such as multiple sclerosis, with NMDA receptor antagonists have been identified[82].

A recent qualitative systematic review on dextromethorphan[83] concluded that it has the potential to be a safe adjunctive agent to opioid analgesia in postoperative pain management. Ketamine is the most studied NMDA receptor antagonist in clinical pain trials, and is commonly used for the treatment of refractory cancer pain, and as an opioid-sparing drug in the treatment of acute postoperative pain, although it is not licenced for these uses. Using drugs beyond licence in palliative care and in the management of refractory pain is both common and necessary[84], however the aim should be to use techniques with documented efficacy.

1.3 Evidence

1.3.1 What is evidence-based medicine (EBM)?

The British epidemiologist Archie Cochrane, and the Canadian epidemiologist David Sackett, are credited with establishing what is now known as evidence-based medicine (EBM). In 1972, Cochrane published a classic text where he suggested that, since resources are limited, they should be used to provide those forms of health care which have been shown in properly designed evaluations to be effective. In particular, he stressed the

importance of using evidence from randomised controlled trials, because these were much more likely to provide reliable information than other sources of evidence[85].

In 1979 Cochrane called on physicians to assemble " a critical summary, adapted periodically, of all…relevant randomized controlled trials"[86]. In the 1980's, a body of systematic reviews in pregnancy and childbirth were produced at the National Perinatal Epidemiology Unit in Oxford[87]. The Cochrane Collaboration was later founded in 1993 and is an international, independent, non-profit organisation devoted to tracking down, evaluating and synthesising RCT's in all areas of medicine. This process centres on the production and dissemination of systematic reviews of healthcare interventions.

1.3.2 Systematic reviews

A systematic review is a review of a particular subject performed in a thorough and systematic manner so that the *risk of bias* is reduced. Systematic reviews and large randomised trials constitute the most reliable sources of evidence for the benefits and harms of a specific treatment (table 3).

Table 3. Type and strength of efficacy evidence
(Adapted from Bandolier,accessed 3rd March 2006)

I	Strong evidence from at least one systematic review of multiple well-designed randomised controlled trials
II	Strong evidence obtained from at least one properly designed randomised controlled trial of appropriate size
III	Evidence obtained from well-designed trials without randomisation, single-group pre-post, cohort, time series, or matched case-controlled studies
IV	Evidence from well-designed non-experimental studies from more than one centre or research group
V	Opinions of respected authorities, based on clinical evidence, descriptive studies, or reports of expert committees

A systematic review involves a comprehensive search and examination of all available published literature on a specific topic followed by extraction of RCT's, and subsequently a critical evaluation of study quality and validity, with exclusion of trials not having high scientific quality.

Quantitative and qualitative systematic reviews

It is not always possible or advisable to pool data from different trials. For example, if the trials have used different outcomes, or have followed the patients for different lengths of time, then combining the results may lead to faulty conclusions. A systematic review where it was not possible to pool data from different trials is termed a *qualitative review.* The result of this type of review then depends upon "vote- counting", assessing whether the result of a trial comparing treatment A to treatment B was "positive" (showing that A is better than B), or "negative"(showing no difference between treatments).

Where possible, information from many trials is statistically combined (*meta-analysis).* A systematic review which includes meta-analysis is termed a *quantitative systematic review*. Quantitative systematic reviews often present the result of meta-analyses in statistical terms such as odds ratio (OR) or weighted mean difference (WMD), which are difficult concepts to relate to clinical practice. In Cochrane reviews it is usual to present the results of meta-analysis in the form of a Forest plot which graphs odds ratios (with 95% confidence intervals) from several studies. Two tools, L'Abbe plot [88] and the number needed to treat (NNT) / number needed to harm (NNH)[89 90], make the results of meta-analyses more accessible.

Systematic reviews: sources of bias and limitations

Interpreting a systematic review has its own pitfalls. Two systematic reviews on the same topic can come to different conclusions. This is usually related to the methods of the review, which may differ, and this may be very confusing for the clinician. In 1996 a systematic review of the methodology used in systematic reviews of analgesic interventions found that most had methodological flaws, and that poor quality systematic reviews reached significantly more positive conclusions[91].

Systematic reviews are themselves subject to bias, and a review is only as good as the data upon which it is based and the methods it uses. The reviewer may be biased, therefore a systematic review should have more than one author, and the authors should be equally involved in the assessment of trials, and in choosing which trials should be included in the review. The selective publication of studies with positive outcome, is another potential source of bias (*publication bias*) which can lead to overestimation of treatment effect in meta-analyses[92]. Expert opinion has previously advised that funnel plots should be used to check for publication bias, with absence of publication bias providing symmetry and the presence of publication bias asymmetry. An empirical evaluation has now demonstrated that asymmetry exists in funnel plots with or without publication bias[93].

Including trials of low quality /validity and excluding trials which are published in other languages than English, are other potential sources of bias. Furthermore, systematic reviews need to be regularly updated, as the trial literature accumulates. Moher et al have recently proposed a definition of what should constitute an appropriate update[94].

The methods of the review determine the reliability, and these should be transparent. Oxman and Guyatt[95] have suggested a quality index by which to assess scientific reviews. More recently, the Quality of Reporting of Meta-analyses (QUOROM)[92] statement was published, providing guidelines for the reporting of meta-analyses of clinical randomised controlled trials.

1.3.3 Trial assessment for inclusion in systematic reviews: quality and validity

Methodological rigour is an essential element of the evidence-based medicine approach, an important objective being to as far as possible eliminate sources of bias. Bias may be defined as "*a one-sided inclination of thought, a prejudice, or any special influence that sways a decision*" [96]. Randomised, double-blinded, controlled trials (RCT's) are designed to eliminate or minimise selection and observer bias.

In designing or assessing a clinical trial the following factors are important:

a. randomisation and allocation concealment

To avoid selection bias, patients in clinical trials should be allocated at random to the different study groups. The process of randomisation should be appropriate, and described in the trial report and the details of allocation assignment should be concealed until the time of allocation [1 97]. Non-randomised studies overestimate treatment effect by 41% [97].

b. blinding

Blinding is necessary to avoid observer bias. Trials that are not double-blind overestimate treatment effect by 17%[97].

c. control

The control group reflects what happens without treatment and /or how a new treatment compares with an established treatment. Several factors can contribute to what happens in the control group (table 4).

Table 4: Sum of effects in the control group (adapted from Kalso et al [98])

Control	**Effects**
Waiting list	Natural course of disease minus the effect of nothing being done (potentially negative effect)
Visits without treatment	Natural course + patient interaction with doctor/ nurse
Placebo treatment	Natural course + interaction + expectation of effect
Active control	Natural course + interaction + expectation + actual effect

Table 4 illustrates the importance of an appropriate control group if we are to find out about the actual effect of a treatment.

The placebo

Ideally, clinical studies of pain treatment should include a placebo and an active control group. The placebo effect is particularly important in studies of pain, since people in pain respond to placebo[99]. The placebo analgesic response is highly variable and cannot be predicted, therefore a placebo group is usually needed in order to show the effect of an analgesic treatment.

Beecher described the placebo as a *"tool to get to certain fundamental mechanisms of the actions of drugs, especially those designed to modify subjective responses"*[99]. He recorded the effects reported by postoperative patients receiving placebo treatment, including both

pain relief and adverse effects and concluded that "*the placebo effect of active drugs is masked by their active effects* " and that "*the power attributed to morphine is presumably a placebo effect plus a drug effect*"[99].

As shown in Table 4, the placebo effect may be considered the sum of patient expectations and patient/ health care worker interaction. A large number of studies have investigated the placebo effect which has proved to have a variable responder rate[100 98]. There has been much discussion regarding the use of placebo controls in medical trials. A placebo control can often provide the clearest insight into what a treatment can accomplish, especially in relation to a subjectively perceived condition such as pain. It is common to use placebo controls in acute pain and chronic non-cancer pain trials.

e. group size

The main cause of variability in response to pain treatment in clinical trials is most likely to be random chance [101]. Small trials may overestimate treatment effect by about 30% [101 102].

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Assessment of quality and validity in clinical pain trials

In the case of assessment of clinical pain trials for inclusion in systematic reviews, specific tools such as the Oxford quality scoring system for controlled trials[103] and the Oxford Pain Validity scale (OPVS)[104] have been developed. The Oxford quality scoring system is a three-item (1-5) scale which evaluates randomisation/allocation concealment; details of blinding measures, and withdrawals and dropouts, providing an overall quality score.

A study may have high quality, but yet have poor validity, lacking adequate trial design to answer the research question. The OPVS is a 5 item (1-16) scale developed to measure

validity of findings from randomised controlled trials, and to enable ranking of trial findings according to validity within qualitative systematic reviews. The OPVS is designed to be used for randomised trials with at least 10 patients per group, and includes 5 items for assessment: blinding, size of trial groups, outcome measures, baseline pain and internal sensitivity, and data analysis. Internal trial sensitivity is important. There must be enough baseline pain in order to detect a difference between baseline and post-treatment pain, and the trial design should be able to detect a difference between groups, should there be one. One way of doing this is to have an additional active control group which shows a significant difference from placebo[105].

1.3.4 The application of EBM to healthcare

Evidence-based medicine is intended applied in the context of clinical experience and critical judgement. The practical application of EBM requires a combination of scientific facts with value judgements and must take into consideration other important factors such as patient preferences and available resources[105].

"The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence…Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough."[106]

Views on EBM are polarised, issues of contention including the limitations of efficacy data from randomised trials as evidence, and concerns regarding the use of the concept of clinical

evidence and guidelines to restrict physician autonomy. Some clinicians feel that EBM ”casts a cold light ” over their clinical practice[107], or that it is reductionistic and dogmatic.

The number of systematic reviews in pain relief in the Cochrane database is steadily increasing. Another useful source of systematic reviews in pain relief is the Bandolier [108]/Oxford Pain Internet Site[109]. In some areas of medicine it is difficult or impossible to investigate specific treatments in the context of a randomised controlled trial. For example, in the field of interventional pain treatment, there are virtually no RCTs. This is due to methodological difficulties, or to other factors hindering research. When this is the case, treatment should at least occur in the context of clinical audits with uniform standards and assessments. Audits can provide data on safety issues, but not reliable efficacy data. The way data from audits are reported and presented is therefore important. Well conducted audits can lead to quality improvement of treatment[1].

In carrying out a systematic review, it soon becomes apparent how difficult it is to perform good clinical pain research and how vital it is to establish uniform standards of quality. Systematic reviews by necessity focus on the need for rigorous clinical trial methodology. It has even been suggested that the most important role of EBM is to sharpen and define the clinical research agenda. The CONSORT (Consolidation of Standards for Reporting Trials) initiative has established standards for the reporting of clinical trials[110]. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), has developed recommendations for core outcome domains[111] and measures[112] in chronic pain trials in order to encourage more complete reporting and to facilitate comparison and pooling of data.

1.4 Methodology

1.4.1 General

Pain is an individual and subjective experience influenced by physiological, psychological and contextual factors. This makes pain difficult to investigate in the context of a controlled clinical trial. What should we be measuring in clinical pain trials, and which factors should be assessed or attempted controlled?

Trials should be *randomised* to control for selection bias, and *double-blinded* to control for observer bias. If possible, there should be a *placebo group* to control for the factors summarised in table 4. The trial should have sufficient *power* to detect a difference between treatment groups. The required *trial size* depends on the size of the effect, and on how sure of the result we need to be. For a clinically relevant result, an estimate of the size of the difference between treatment and placebo is needed. If the treatment effect is weak, and/or there is considerable variability in the levels of pain, then larger numbers of patients will be required to demonstrate a clinically relevant treatment effect[101]. Acute pain trials traditionally use only about 40 patients per arm[101], while in cancer pain groups are usually even smaller. One way around the problem of trial size is standardisation of trial design and pooling data from multiple trials of small size (meta-analysis). Alternative measures of analgesic efficacy suitable for large-scale trials (”mega-trials”) have also been suggested. For example a simple global subjective efficacy rating (”How effective do you think the treatment was?) has been shown to provide similar measures of analgesic efficacy as total pain relief (TOTPAR) derived from hourly measurements[113].

Trial *sensitivity* is an important issue. In order to show a difference between treatments reducing pain intensity, there should be *sufficient baseline pain intensity* [114]. A systematic

review of randomised trials investigating the effectiveness of intra-articular morphine in arthroscopic procedures of the knee joint found that only 15 of 25 trials were sensitive, and that a minimum of 30% of the maximum possible pain intensity is needed for an analgesic effect to be detected in a study[115]. The question of analgesic *dose* is also relevant- in the same systematic review it was found that most studies with positive outcome had used higher doses than the negative studies[115].

Common *outcomes* in pain trials include pain intensity assessed using subjective, validated measures of pain on movement and at rest e.g., visual analogue scale of pain intensity (VASpi) or other validated scales, and/ or pain relief. The commonest tools to measure pain intensity and pain relief are categorical and visual analogue scales. Categorical scales are quick and simple, however, the limited number of choices may make these less sensitive than VAS and numerical scales[116]. Pain relief scales have the same baseline relief value (zero) and are therefore easier to compare and possibly more sensitive than pain intensity scales [1]. If rescue medication is given, then total consumption of *rescue medication* may be an appropriate outcome[115]. Another useful outcome is *time to remedication* which gives an estimation of analgesic duration. All pain treatment is a question of balancing effect and adverse effects. Major and minor *adverse effects* are therefore important outcome measures, and where possible should also be reported as *dichotomous data*, thus enabling meta-analysis. Specific guidelines for reporting adverse effect information in clinical trials have been published[117].

Recommendations have been made for core outcomes and measures in trials of chronic pain[111 112], while specific consensus recommendations for trials in acute and cancer pain are lacking. For chronic pain trials six core outcome domains are recommended: (1) pain, (2)

physical functioning, (3) emotional functioning, (4) participant ratings of improvement and satisfaction with treatment, (5) symptoms and adverse events, (6) participant disposition (adherence to the treatment regime, reasons for withdrawal from trial). The Beck Depression Inventory (BDI)[118] and the Profile of Mood States (POMS)[119] are recommended as core outcome measures of emotional functioning in chronic pain.

1.4.2 Acute pain trials: special issues

Nociceptive pain is most common in the acute setting, but neuropathic pain due to nerve injury may also be present. The usual model for acute pain is pain after surgery. Stubhaug and Breivik[114] have described issues of importance for acute postoperative pain trials. Acute pain occurs within a defined time frame and acute pain trials are of short duration. Parallel group studies are the most common, while selected crossover studies may be performed in patients undergoing repetitive uniform surgical interventions such as wisdom tooth extraction. A crossover design has the advantage that the patient is his/her own control. Sufficient baseline pain (trial sensitivity) is important. If patients are given an analgesic treatment before an initial pain level can be established (for example in the case of preemptive analgesia), the results will be difficult to interpret. Not all patients require analgesia after surgery, and this type of design may lead to patients not needing analgesics being included in the trial.

Polypharmacy is common in the perioperative period and it is therefore important to standardise the anaesthetic regime as much as is feasible. Single dose analgesic studies are easy to perform and often used in acute pain. However a single dose study does not closely

mimic the true clinical setting, and adverse effects may be missed[114]. Patient controlled analgesia (PCA) studies are useful, allowing observation over time and measures of analgesic consumption. The limitations of PCA trials include lack of sensitivity, and the number of factors which may influence analgesic consumption in this model, such as bolus size, lockout time, psychological factors and degree of sedation caused by the test drug, thus influencing the patient's ability to administer the analgesic.

Questions of *which drug, timing of administration, and duration of follow-up* are relevant. Stubhaug et al.[114] described the phenomenon of chronic pain after surgery and the need for new methods to study this. Chronic pain after surgery is common [120]. The concept of preemptive analgesia was described by Woolf et al in 1993 [121]. Preemptive analgesia is initiated before and during the surgical procedure with the aim of reducing nociceptive input and preventing or limiting central sensitisation. Studies on preemptive analgesia have however proved inconclusive, and it is now recommended that future studies should redirect their focus from the *timing* of perioperative analgesia to *"protective" analgesia*[122], using different types of drugs such as NMDA receptor antagonists or gabapentinoids, with the aim of preventing hypersensitivity to pain[123]. The following have been suggested as appropriate requirements for studies of chronic postoperative pain: preoperative data including assessment of pain and psychological risk factors for chronic pain; description of the operative process; assessment of acute postoperative pain and management and standardised follow-up at intervals to one year or more[120 123].

1.4.3 Cancer pain trials: special issues

In palliative care there are special methodological issues related to clinical pain research. For example, it may be difficult to recruit patients to trials due to inclusion criteria, and dropout rates are high. There may be high rates of anxiety and or depression in this patient population.

Cancer patients require analgesic drug treatment over long periods of time. Trials are however usually of relatively short duration due to disease progression and high rates of withdrawal. Cancer patients often receive other types of treatment which may reduce, or increase pain during an analgesic trial. These potentially confounding factors must be considered when deciding inclusion and exclusion criteria for a trial. Cancer pain trials traditionally have small numbers of patients.

Many analgesic trials in cancer pain are *equivalence studies*, comparing two formulas of the same drug. There are a number of methodological issues concerning equivalence trials[124]. The first issue concerns the use of an *active comparator*. The assumption when using an active comparator opioid in a cancer pain trial is that the comparator has previously been shown to be effective in the same context in a randomised double- blind placebo-controlled trial. The second issue concerns the *design* of equivalency trials using an active comparator. The design should as far as possible mirror that of earlier trials demonstrating the comparator's efficacy against placebo[124]. The third methodological issue concerns *trial size*, since equivalency trials generally need to be larger than their placebo-controlled counterparts[124]. The latest revision of the CONSORT statement addresses the particular difficulties of equivalence trials and contains a checklist for reporting this type of trial[125].

The pitfalls of performing equivalence trials in the palliative care patient population are obvious.

The use or non-use of a placebo control in cancer pain trials is controversial. Researchers are generally reluctant to use placebo in opioid trials, preferring to use an active comparator. This decision is based upon the assumption that opioids are effective analgesics in cancer pain, and that it would be unethical to use a placebo control. While it is generally not ethical to use a placebo control in trials of oncological treatment because of the greater risk to the patient due to treatment delay, in trials of the pharmacological treatment of cancer *pain* a placebo control may be both feasible and useful.

The Declaration of Helsinki[126] amendment of 2000 originally stated that the placebo should be used prudently in research trials, and only in cases where there was no proven therapy for the condition under investigation. In a situation where there already exists an effective treatment (that is a drug shown to be effective when compared to placebo), it was recommended to use the active comparator as a control. Following considerable polemics, the World Medical Association (WMA) subsequently published a clarification of this statement, where it was agreed that there were circumstances where a placebo-controlled trial might be ethically acceptable, even if proven therapy was available. In the clarification statement of 2002, it is stated that the use of placebo control could be justified

" where for compelling and scientifically sound methodological reasons its use was necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or where a prophylactic, diagnostic or therapeutic method was being investigated

for a minor condition and the patients who received placebo would not be subject to any additional risk of serious or irreversible harm."

"*Scientifically sound methodological reasons*" is a key phrase in this statement. Concurrent with the need for high ethical standards is an equally important need for scientific rigour. Exposing patients to large numbers of trials having considerable methodological limitations, and the potential for producing unreliable data, may also be considered unethical.

In summary, despite the obvious difficulties associated with clinical pain research in the palliative care patient population it is important to maintain high scientific standards and to ensure that research questions relevant to clinical practice are asked. Researchers conducting efficacy trials of pharmacological pain treatment in cancer pain should always consider the feasibility of using a placebo control.

2. Aims of the present study

1. To contribute to existing trial methodology by developing and testing a clinical model where the same patient could serve as her own control, for use in the study of acute and chronic postoperative pain.
2. To prepare a systematic review on postoperative pain with focus on use of the NMDA receptor antagonist ketamine, in order to establish the current evidence base for this practice and in doing so, to assess the methodology.
3. To prepare a systematic review on cancer pain treatment with focus on the use of ketamine as adjuvant to opioid for refractory pain, to establish the evidence base for this practice and, in doing so, to assess the methodology
4. To evaluate the quality and validity of trial methodology used in cancer pain analgesic trials, by performing a systematic review.

3. Methods

Paper I : Eight female patients scheduled to undergo elective bilateral surgery participated. All patients received a standardised general anaesthesia. Breasts were randomised to preoperative infiltration with active treatment (lidocaine and adrenaline), or placebo (saline and adrenaline). Preoperative assessment included (baseline) quantitative sensory testing (QST) using a thermotester, which was repeated postoperatively and after six months, and pain intensity measurement at baseline, at several time points after surgery and at six months. At the same time points, additional sensory testing with brush and von Frey filaments was performed. Pain intensity measurements of breast pain were regularly performed at rest, on coughing and on elevation of the ipsilateral arm, using a visual analogue pain scale (VAS). For the statistical analysis of measurements over time (VAS pain intensity scores), the area under the curve (AUC) was calculated. The difference between saline and lidocaine responses was evaluated using the Wilcoxon signed rank test. $P<0.05$ was considered to be significant.

Papers II, III and IV: Systematic reviews: For papers II and III, comprehensive and systematic searches of the scientific literature were performed by one reviewer (RFB) with assistance from the Cochrane Pain Palliative and Supportive Care Collaborative Review Group, Oxford. For paper III the searches were performed by one reviewer (RFB) and by a researcher at the Pain Management Unit at the Royal National Hospital for Rheumatic Diseases, Bath, UK. All titles were examined by two reviewers (RFB and EK) and potential trials retrieved. In addition, reference lists of relevant textbooks, reviews and trials were

handsearched for possible trials. For papers II and III, the manufacturer of ketamine was contacted for access to published and unpublished data in the PARDLARS database. There was no language restriction. Japanese medical literature was assessed with the help of the Bodleian Library, University of Oxford. Papers in Turkish were assessed with the help of a native speaker. All retrieved trials were assessed for possible inclusion by RFB and two co-reviewers. All trials to be considered for inclusion were assessed for quality using the Oxford quality scale[103] and for validity using the Oxford Pain Validity Scale (OPVS)[104] by RFB and EK, and in the majority of cases together with a third co-reviewer, until consensus was reached. Data was extracted according to pre-hoc decision. Authors were contacted in order to acquire missing data. Meta-analysis was performed where appropriate (Paper II). For dichotomous outcomes, relative risks, and for continuous outcomes, weighted mean differences (WMD), were calculated using RevMan 4.2 software[127]

4. Results and discussion of papers

4.1 Paper I

Bell RF, Sivertsen Å, Mowinckel P, Vindenes H. A bilateral clinical model for the study of acute and chronic pain after breast-reduction surgery. Acta Anaesthesiol Scand 2001; 45 (5):576-582

Results

VAS pain intensity scores: the model demonstrated a clear difference between lidocaine and placebo-treated breasts. The sum of VAS scores for pain intensity was significantly lower in the lidocaine group than in the placebo group for the entire registration period of 10 hrs after surgery. Regarding chronic postoperative pain there was no pain on testing at 6 months, however 3 patients reported ongoing periodic pain. There was no difference between lidocaine and placebo-treated breasts at 6 months.

Quantitative sensory testing: Five patients exhibited large changes in temperature thresholds (±5°C) 11 days after surgery, with no difference between lidocaine and saline-treated breasts. Three of these patients reported ongoing periodic pain at six months, and exhibited significant thermal threshold changes, with no difference between lidocaine and placebo-treated breasts.

Discussion

Chronic pain after surgery is common[120]. Postoperative pain intensity has been shown to be a predictive of chronic postoperative pain[128 129 130], and it has been suggested that preemptive analgesia may reduce the risk of chronic postoperative pain.This has been been demonstrated in several clinical trials [131 38]. The hypothesis of preemptive analgesia was initially received with great enthusiasm, however no major clinical benefits have as yet been documented [132]. Most studies in postoperative pain have focused on pain relief in the early postoperative period, and not on the development of chronic postoperative pain.

The advantageous aspects of the model we describe are that:

1. It is *bilateral*, with the patient serving as her own control.

2. The patients undergo sensory assessment with *QST*, using a thermotester which delivers specific stimuli, testing temperature perception thresholds. QST is thought to be especially valuable in detecting impaired small fibre function which may be a factor in the chronification of acute pain. Quantitative sensory testing systems have been specifically developed to assess and quantify sensory function in patients with neurological symptoms. Perioperative testing with long term follow-up may conceivably contribute to a better understanding of the mechanisms involved in persistent postoperative pain. A report by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology in 2003 concluded that QST is a potentially useful tool for measuring sensory impairment for clinical and research studies[133]. In our study it was interesting to note that the three patients who reported ongoing pain at 6 months also exhibited marked thermal threshold changes.

3. It involves a *long-term follow-up* regarding pain and sensory changes. This is in accordance with recommendations for clinical trials in postoperative pain[114 123].

The limitation of the model is that it is restricted to breast interventions and to the use of a local agent, such as a local anaesthetic.

Dahl and Moiniche[123] have extensively discussed the concept of preemptive analgesia and suggest that the major problem is not nociception, but the prevention of central sensitisation. As suggested in the paper, investigation of longer-lasting local anaesthetic or continuous application would be of interest. Prevention of central sensitisation in the clinical situation may be difficult, and Dahl et al[122 123] recommend that future trials should investigate combinations of different classes of drug, such as ketamine, dextromethorphan or gabapentin, all of which have demonstrated anti-hyperalgesic potential in clinical trials of postoperative pain. It would be interesting to test the effect of *ketamine* in this model since it is thought to have a local effect via peripheral NMDA receptors, and the expression of peripheral NMDA receptors has been shown to increase under conditions of inflammation[17 18]. An animal study has demonstrated that topical ketamine blocks topical morphine tolerance in mice[134]. An experimental study in healthy volunteers showed that local treatment with ketamine inhibits the development of secondary hyperalgesia in a burn model[135]. A randomised, controlled clinical study in postoperative pain also reported peripheral effects of ketamine[136], however the group size in this trial was very small, less than 10 patients per group. A randomised placebo-controlled trial in patients with neuropathic pain syndromes (diabetic neuropathy, postherpetic neuralgia, and postsurgical/ posttraumatic pain) found no difference between 1% topical ketamine and placebo[137].

Since the publication of this paper new drugs, such as *peripheral opioids*, have been developed. The existence of an endogenous peripheral analgesic system is well-documented[22 138]. Using an in-vitro nerve-skin preparation from rats, peripherally delivered opioid (morphine) has recently been shown to directly inhibit the activity of cutaneous nociceptors under conditions of inflammation[139]. A peripheral opioid such as the μ-agonist frakefamide[140] could therefore also be an interesting drug to investigate in this model.

Improving the model

The model could be applied to patients undergoing bilateral breast augmentation which is generally considered to be a more painful procedure than breast reduction and which has been shown be associated with chronic postsurgical pain[130]. This may further improve the sensitivity of the model. As suggested in the paper, time-consuming sensory testing with von Frey filaments, and VAS measurements on coughing could be eliminated, since these provided no additional useful information. Assessment of pain relief in addition to pain intensity, and reporting of patient treatment preference would also improve the model.

Improving the paper- retrospective critical comments

The process of randomisation and allocation concealment should have been described. The number of patients should have been at least 10 (giving a minimum of 10 breasts in each group)[88]. No adverse effects were registered and this should have been stated, together with the method of assessment of adverse effects. The clinical significance of the demonstrated difference in pain scores versus the statistical significance, should also have been discussed.

4.2 Paper II

Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. The Cochrane Database of Systematic Reviews 2006, Issue 1. Art.No.:CD004603. DOI: 10.1002/14651858.CD004603.pub2.

Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain. A quantitative and qualitative systematic review (Cochrane review) Acta Anaesthesiol Scand 2005;49(10):1405-1428

Results

Thirty-seven randomised, controlled trials with a total of 2137 patients, of which 1210 received ketamine, and 53 treatment arms were included. Thirty-two trials used racemic ketamine, four used S(+) ketamine and one used the R(-) isomer. The trials were heterogenous and varied in regard to timing and route of administration and dose of ketamine. Data from 10 trials reporting the same outcome (24hr patient controlled analgesia (PCA) morphine consumption) was combined. The meta-analysis found that ketamine reduced 24hr postoperative PCA morphine consumption. In addition, 26 trials reported nausea and/or vomiting as dichotomous data. Quantitative analysis of this data found that ketamine reduced postoperative nausea and/ or vomiting.

Discussion

Paper II is a quantitative and qualitative systematic review. The objective of the review was to establish the evidence base for the efficacy and tolerability of perioperative ketamine in the treatment of acute postoperative pain. At the commencement of this paper, no systematic review on the topic had been published, however two quantitative and qualitative systematic reviews on perioperative ketamine[141 142] were published during the preparation of the paper. These reviews are briefly mentioned in paper II and will be further discussed below.

That ketamine is a "hot topic" in pain treatment is evidenced by the abundance of reports and trials. A search of PubMed in May 2006 revealed 13 narrative reviews, a literature review based on an electronic search of the MEDLINE database from 1966-1998 [143] and five systematic reviews on ketamine for pain treatment, including papers II and III. In addition, there were six narrative reviews on NMDA receptor antagonists for pain treatment and one qualitative systematic review on NMDA receptor antagonists in "preventive analgesia".

In the qualitative systematic review[144] on NMDA receptor antagonists for 'preventive analgesia', the authors searched MEDLINE and EMBASE for randomised, double-blinded trials of NMDA receptor antagonists given during the perioperative period. The trials were assessed for quality using the Oxford Quality scale[103]. The primary outcome to be considered was 'preventive analgesia', defined as analgesia beyond five half lives of the drug under examination. The conclusions of the review were that '*both ketamine and dextromethorphan produced a significant preventive analgesic benefit in 58% and 67% of studies, respectively'*.

Schmid et al[143] investigated low-dose ketamine for postoperative pain. This review was based on a search of MEDLINE with search strategy not described. Twenty-eight randomised, prospective, controlled double-blind trials reporting pain scores were included, but were not subjected to quality and/ or validity assessment. A number of these trials were excluded by our own review due to methodological problems. The conclusions of this review were that '*ketamine may provide clinicians with a tool to improve postoperative pain management and to reduce opioid related adverse effects'*.

Comments on the meta-analysis

Efficacy data

The finding of the quantitative analysis, that perioperative ketamine reduces 24hr PCA morphine consumption needs to be interpreted in the light of several factors. The ketamine regimes being compared in these trials differed (table 5).

Table 5. Trials included in the meta-analysis for efficacy

Trial	**Surgical procedure/ ketamine**
Roytblatt 1993	Elective open cholecystectomy /Preincisional bolus of ketamine 0.15 mg/kg IV
Javery 1996	Lumbar microdiscectomy / Postoperative IV PCA ketamine 1 mg/bolus
Stubhaug 1997	Nephrectomy (live kidney donors) /Ketamine bolus 0.5 mg/kg IV + infusion 2 mcg/kg/min IV for 24 hrs from start of study
Ilkjær 1998	Elective nephrectomy or operation on pelvic structures / Ketamine bolus 10 mg IV before surgical incision/10 mg/h IV postoperative infusion
Adriaenssens 1999	Laparotomy / Ketamine IV infusion, initially 10 mcg/kg/min for 48 hours after surgery
Menigaux 2000 (2 ketamine treatment arms)	Knee surgery: elective arthroscopic / 1. Preincisional ketamine bolus 0.15 mg/kg IV

	2. At wound closure: ketamine bolus 0.15 mg/kg IV
Guignard 2002	Abdominal surgery / Ketamine bolus 0.15 mg/kg IV + infusion 2 mcg/kg/min IV from prior to incision until skin closure
Jaksch 2002	Elective arthroscopic anterior cruciate ligament repair / S(+) ketamine bolus 0.5 mg/kg IV + infusion 2mcg/kg/hr IV until 2 hours after emergence from anaesthesia
Guillou 2003	Major abdominal / After surgery: initial ketamine bolus 0.5 mg/kg IV + infusion 2mg/kg /min IV for 24 hr and 1mg/kg/min IV from 24-48 h
Snijdelaar 2004	Radical retropubic prostatectomy / Intraoperative S (+) ketamine bolus 0.1 mg/kg IV, followed by continuous infusion of 0.002 mg/kg/min IV until skin closure+ post-operative IV PCA S (+) ketamine 0.5 mg bolus

The advisability of combining data from trials which use different timing, duration and route of administration of ketamine may be questioned. Eight of the included trials used racemic ketamine, and two used S(+) ketamine. In the absence of more homogenous trials, a common denominator was found in that all ten trials report the same outcome. The conclusions are therefore limited, and issues relating to dose, timing and route of administration unresolved.

Two quantitative reviews on ketamine for postoperative pain were published during the preparation of our review on the same topic. Elia et al[142] chose to restrict quantitative analysis to a "clinically homogenous" subgroup of 16 trials examining intravenous bolus and/ or infusions of ketamine in patients undergoing general anaesthesia. Cumulative morphine consumption at 24 hours based on data from four trials gave similar results to our own analysis of 24hour PCA morphine consumption in 10 trials. Subramaniam et al[141] performed quantitative analysis of VAS data from four subgroups stratified according to

route of administration, but did not perform quantitative analysis of data concerning morphine consumption.

An interesting observation in our data was the fact that increasing the dose of ketamine above an estimated dose of 30 mg/ 24 hours did not appear to increase the morphine-sparing effect. Since the adverse effects of ketamine are dose-dependent, it could be speculated that the true clinical potential of ketamine in pain treatment lies in the use of low doses, adjuvant to opioid, since concurrent administration with opioid has been shown to increase the distribution of ketamine into the brain[66].

Tolerability data

Two trials did not report on adverse effects. Twelve trials did not report dropouts/ withdrawals. The quantitative analysis of the combined nausea and/or vomiting data from 26 trials indicated that ketamine reduces PONV. The data was again heterogenous, with the methods of assessment of adverse effects differing between trials (table 6). Different methods of collecting adverse events can produce different results[117]. The results of the meta-analysis should therefore be interpreted with this in mind and may be compared with the findings from the other two systematic reviews on perioperative ketamine. Elia et al[142] performed quantitative analysis on dichotomous data from five trials reporting nausea, four trials reporting vomiting and three trials reporting nausea or vomiting, and found no significant difference from control. Subramaniam et al[141] performed quantitative analysis regarding the incidence of nausea and vomiting on data from 16 trials and found " a trend towards less PONV in ketamine-treated patients compared with patients who received opioids alone".

Table 6. Post-operative nausea and/ or vomiting (PONV): method of assessment in trials included in meta-analysis

Trial	PONV:method of assessment
Roytblatt 1993	”Reported if present”
Lauretti 1996	Direct questioning (VAS 0-10)
Stubhaug 1997	Direct questioning (VRS 0-3)
Abdel-Ghaffar 1998	Not stated
Chia 1998	Not stated
Adriaenssens 1999	Direct questioning
Hercock 1999	Direct questioning (NRS)
Suzuki 1999	Direct questioning (VAS)
Tan 1999	Regularly ”assessed”
Kirdemir 2000	Not stated
Menigaux 2000	”If present….noted”
Himmelseher 2001	”noted”
Menigaux 2001	Regularly ”recorded”
Papaziogas 2001	Direct questioning
Subramaniam (a) 2001	Direct questioning
Subramaniam (b) 2001	Direct questioning
Guignard 2002	”Recorded”
Jaksch 2002	”Recorded”
Santawat 2002	Direct questioning (VRS 0-3)
Guillou 2003	Not stated
Kararmaz 2003	Direct questioning (VRS 0-3)
Xie 2003	”Observed”
Unlugenc 2003	”Recorded”
Argiriadou 2004	”Noted”
Kakinohana 2004	”Recorded”
Snijdelaar 2004	Direct questioning (nausea: VAS 0-10; vomiting: present or absent)

VAS: visual analogue scale
NRS: Numerical rating scale
VRS: verbal rating scale

Methodological issues

In general, the quality and validity scores in these trials were high. The included trials used either a placebo control, or a ”placebo-like” control- (morphine versus (morphine + ketamine)). Polypharmacy is common in the perioperative period, and it was attempted to standardise anaesthetic regimes and postoperative pain treatments as far as possible. The standard of reporting was generally good, except with regard to adverse effects as mentioned

above. Group sizes were generally small and there was considerable heterogeneity of ketamine treatment regimens. The largest group of studies investigated a preincisional bolus, and/ or a perioperative IV infusion of ketamine, and it is suggested that future trials could focus on this route and duration of administration. Finally, the question of chronic postoperative pain is yet to be addressed. Only one included trial had a long term (up to 12 months) follow-up[145].

Several randomised, controlled trials on perioperative ketamine for acute post-operative pain[146 147 148 149] have been published since this Cochrane review and it will be interesting to see what information the accumulating data provides.

4.3 Paper III

Bell R, Eccleston C, Kalso E. Ketamine as adjuvant to opioids for cancer pain. The Cochrane Database of systematic reviews 2003, Issue 1. Art No.:CD003351. DOI:10.1002/14651858. CD003351

Bell RF, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. A qualitative systematic review. J Pain Symptom Manage 2003;26;3:867-875

Results

Four randomised, controlled trials met the inclusion criteria. Two were excluded due to methodological flaws. Both trials concluded that ketamine improves the effectiveness of

morphine in the treatment of cancer pain. Pooling of data was not appropriate due to the small number of patients and and the presence of clinical heterogeneity. Some patients experienced hallucinations on both ketamine plus morphine, and morphine alone. No other serious adverse effects were reported.

Discussion

Ketamine is widely used as an adjuvant to opioids for the treatment of refractory cancer pain and the treatment is described in leading textbooks on pain treatment and palliative care[150] [151]. This is a qualitative systematic review with the objective of establishing the evidence-base for this practice. No other systematic review on this topic has been published.

Efficacy and tolerability data

Only four RCTs were identified and the data was heterogenous. Of the two included trials, one lasted only hours and investigated the effect of intravenous ketamine, while the other lasted weeks (exact duration not given) and studied the effect of intrathecal ketamine.

In addition to the four RCT's, a number of open-label studies and case reports were retrieved. While case reports cannot provide efficacy data, they can be a source of useful information on adverse effects. In general adverse effects were not reported as severe. Hallucination and sedation were the most commonly reported and were related to higher doses of ketamine. Two case reports described toxic effects of continuous spinal administration of ketamine over 7-21 days[72] [73]. An additional case report was recently published describing good pain relief but severe histological abnormalities of spinal cord

and nerve roots after continuous intrathecal administration of S(+) ketamine in a patient with intractable cancer pain[74]. One case report also described acute generalised hyperalgesia in a patient following abrupt cessation of a several week long subcutaneous infusion of ketamine 120-200 mg/ 24 hours[152]. Inflammation of the needle site during subcutaneous infusion has also been reported as a common problem[152 153 154].

Since the preparation of this review further case reports[155 156 157] and a retrospective audit[158] have been published, representing different countries including Turkey, the Netherlands, Canada and Italy. From the literature it is evident that ketamine is used primarily for the treatment of refractory pain and that clinicians consider it to be a useful drug in this setting. Indeed, paper III provoked a disappointed reaction from a group of experienced clinicians[107 159].

Methodological issues

Both included trials had very small numbers of patients, 10 in one trial and 20 in the other, and both employed a crossover design. One trial used a placebo control, while the other used a "placebo-like" control (morphine versus morphine plus ketamine). The two excluded trials were from the same research group and were considered to have flawed methodology, employing a fixed maximum dose of rescue morphine, and morphine consumption as outcome.

Given the widespread use of ketamine in the palliative care setting, this qualitative systematic review indicates a need for well-designed, randomised, placebo-controlled trials. Future RCT's on ketamine as an adjuvant to opioids for cancer pain should be looking at

efficacy, adverse effects and optimal dose and route of administration. Since sedation is a commonly reported adverse effect in case reports of ketamine as adjuvant to opioid, the question of effective trial blinding is relevant. This could be achieved by using an active comparator (for example a low dose of midazolam), in addition to a placebo control. Alternatively, direct questions could be made to investigator and patient in order to check for blinding. Patient treatment preference would also provide important information.

The literature demonstrates widely differing clinical practice concerning ketamine dose and route of administration. From the case reports it appears that the use of ketamine as a subcutaneous infusion is common practice. However, providing the cancer patient is able to take oral medication, this route of administration is generally preferred[45]. The use of oral ketamine as an adjuvant is poorly documented. Several case reports and an open label study[160] report that it is effective in neuropathic pain states, but that adverse effects such as drowsiness and nausea are common. N of 1 randomised, controlled trials of oral ketamine in patients with chronic pain found that oral ketamine gave increased analgesia in only three of 21 patients and that adverse effects limited use in approximately 50%[161]. In an experimental study in healthy volunteers, using an acute burn model, oral ketamine had no effect on secondary hyperalgesia or thermal and mechanical pain thresholds[162]. Racemic ketamine has an oral bioavailability of only 17 %[64] due to high first passage metabolism. Other possible routes of administration are intranasal[65] and sublingual. A case series reporting the use of sublingual ketamine for breakthrough cancer pain has recently been reported[157].

4.4 Paper IV

Bell RF, Wisløff T, Eccleston C, Kalso E. Controlled clinical trials in cancer pain. How controlled should they be? A qualitative systematic review. Br J Cancer 2006;94:1559-1567

Results

Thirty-four randomised, double-blinded, controlled trials on specific oral opioids (morphine, hydromorphone, oxycodone) for cancer pain were included. The total number of patients enrolled was 1864. Only one study had a placebo control (nine patients, duration 12 hours) and one study had a placebo arm in the first phase (four patients, duration 7±1 days). Thirty-three of the thirty-four trials were equivalence trials. Only nine trials were scored as sensitive. More than 50% of the trials did not report performing power calculations. Only 11 trials included a description of the pain. The criteria for adequate/ inadequate pain relief was clearly defined in only eight trials and no two studies used the same criteria. Only three trials assessed and reported psychological variables.

Discussion

Several systematic reviews[163-165] and two comprehensive evidence report/ technology assessments[166 167] have remarked on the methodological shortcomings of opioid trials in cancer pain. In addition, Caraceni et al[168] have reviewed cancer pain assessment in clinical trials in oncology published between 1999 and 2002. A search of PubMed performed in May 2006 using the terms: *trial methodology AND opioid AND cancer* and limited to “Reviews” found 14 hits, none of which primarily concerned trial methodology. This paper has identified a number of methodological problems and possible areas for improvement in the

cancer pain analgesic trial literature. The general lack of a placebo control in these trials raises an interesting question.

Opioids for cancer pain- what is the evidence?

Oral morphine is the ”gold standard” opioid for the treatment of cancer pain. In this review of trials investigating oral opioids for cancer pain, only one trial had a placebo control, while another trial had a placebo control in the pilot phase of the study. In the first of these trials which investigated the effect of a loading dose of morphine elixir added to the first dose of slow-release morphine tablets, a total of *nine* patients were treated with a single dose of placebo, the study duration being 12 hours[169]. In the pilot phase of the second trial, where three different formulations of slow-release morphine were compared to placebo for 7±1 days, a total of *four* patients received placebo treatment[170]. The assumption for using morphine as an active comparatoror in the remaining trials is that it has previously been found *effective in cancer pain compared to placebo.* But is this the case?

A Cochrane review concluded that oral *morphine* is effective for cancer pain[164]. This review attempted to bring all of the literature together and included data from randomised trials, including open label trials. The authors remarked that the majority of trials are equivalency studies designed to show that different formulations of morphine have the same effect, and that this makes it difficult to extract information on the effectiveness of morphine *per se*. Furthermore, they underlined that it is unclear whether the trials are sufficiently powered to detect a clinically meaningful difference between treatments. Although the Oxford Quality Scale scores were generally high, with a median of 4, it was noted that the quality of reporting was disappointing, especially in regard to assessment of pain and pain relief. The

trials in this review were not scored for validity, and the relevance of a placebo control for the demonstration of efficacy is not specifically addressed.

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In a second Cochrane review[163], 11 trials investigating *hydromorphone* in cancer pain were included, all of which used an active comparator. A recent quantitative systematic review on *oxycodone* for cancer pain[165] found no placebo controlled trials. An Agency for Healthcare Research and Quality (AHRQ) Evidence Report[166] looking at the relative efficacy of analgesics in cancer pain described the need for placebo controls in order to avoid overestimation of treatment effects, at the same time noting that placebo controls in cancer pain trials are ”rare”. More recently, a report by the Norwegian Knowledge Centre for the Health Services[167] concluded that opioid analgesics ”have good effect on moderate to strong cancer pain”. According to this report, ”*the general impression from all the studies is that opioids are extremely effective in relieving pain in cancer patients”* this being *”documented in old placebo-controlled studies.*” No references were provided in support of this statement. In order to obtain the specific references, the authors of the report were contacted, and subsequently clarified that the statement pertains to references in the AHRQ report [166]. A closer examination of the AHRQ references did not provide any supplementary placebo-controlled trials investigating *oral morphine for cancer pain*. Table 7 is a summary of placebo-controlled trials investigating stronger opioids for cancer pain.

Table 7: Randomised, double-blind trials in cancer pain patients comparing stronger opioid with placebo

Study	N=	Drug	Route	Duration	Comments
Houde et al. 1960 [171]	67	Morphine	IM	6 hours	Double-blind Crossover Single dose
Stambaugh et al. 1982 [172]	29 (20 evaluable)	Butorphanol Acetaminophen B+A	PO	Up to 6 hours	Double-blind Crossover Single dose
Stambaugh et al 1983 [173]	30	Meperidine Hydroxyzine M+H	IM	4 days, 1 treatment per day	Double-blind Crossover Single dose
Stambaugh et al 1987a [174]	60 (3 groups)	Dezocine Butorphanol	IM	7 days	Double-blind Parallel group Single and multiple dose
Stambaugh et al. 1987b [175]	43 (40 evaluable)	Ciramadol Codeine	PO	6 hours	Double-blind Crossover Single dose
Hoskin et al. 1989 [169]	20 (19 evaluable) 9 treated with placebo	Morphine	PO	12 hours	Double-blind Single dose Parallel group
Broomhead et al 1997 [170]	172 (152 final day efficacy data) 4 treated with placebo	Morphine	PO	7±1 days	Double-blind Parallel group Placebo control only in first phase of study
Farrar et al. 1998 [176]	92 (89 assessable, treated with at least one unit of OTFC and one unit of placebo)	fentanyl citrate (OTFC)	OTM	Titration period + 10 randomly ordered treatment units (Pain evaluated for 60 minute period)	Double-blind Crossover Multiple dose Breakthrough pain

IM: intramuscular; PO: oral; OTM:oral transmucosal

Sources: AHRQ nr. 35[166], Wiffen et al[164] Quigley[163], Kongsgaard et al[167], Reid et al[165] and Bell et al (paper IV). In addition, searches were performed on PubMed with limits ”randomised controlled trial” and search terms : ”fentanyl AND placebo and cancer” / ”methadone AND placebo AND cancer”.

Unless there is a body of data we have been unable to access, these findings raise interesting questions regarding the current efficacy data for oral opioids in cancer pain. Even though opioids appear clinically effective for cancer pain, the question of *how* effective is not resolved by the literature. Morphine is accepted as the gold standard for cancer pain treatment, however placebo-controlled efficacy data in cancer pain is lacking.

In addition to the issue of placebo control, this paper identifies a number of areas where methodology in cancer pain drug trials could be significantly improved. In the included trials the pain being treated was rarely described, and only a minority of trials defined the criteria for treatment effect. Emotional functioning, including assessment of depression and anxiety, is a recommended core outcome domain and measure for chronic pain trials [111 112]. However, in the cancer pain trials, psychological factors were generally not addressed. The majority of trials were equivalence studies. The limitations of this type of trial have recently been addressed in the revised CONSORT statement[125]. Finally, the importance of investigating clinically useful outcomes should be emphasised. We need to know which patients respond to opioids and which patients do not respond, rather than whether two formulations of the same opioid are equally effective.

5. Conclusions

Aim 1*: To develop and test a clinical model for use in the study of acute and chronic postoperative pain*: A bilateral clinical model which is sensitive, and suitable for investigating specific local interventions for acute and chronic postoperative pain was tested and reported in paper I.

Aim 2*: To investigate the current evidence-base for perioperative ketamine in acute postoperative pain by preparing a systematic review, and by doing so, to assess the trial methodology.* Paper II is a quantitative and qualitative systematic review. The results of the meta-analysis provides level 1 evidence that ketamine reduces morphine requirements in the first 24 hours after surgery, and reduces postoperative nausea and vomiting. Adverse effects were mild or absent. The data is heterogenous and cannot be translated into a specific treatment regime. The quality and validity scores of the individual trials were generally high, however there was considerable clinical heterogeneity. Issues of optimal dose, timing and route of administration of ketamine are not resolved by the current literature.

Aim 3*: To investigate the current evidence-base for ketamine as an adjuvant to opioid for cancer pain, and in doing so, to assess the trial methodology*: The current evidence is insufficient to make conclusions regarding the benefits and harms of ketamine as adjuvant to opioid for cancer pain. Conclusions regarding trial methodology were not possible due to the limited number of trials. A large number of clinical case reports demonstrate widely varying practice with regard to dose and route of administration.

Aim 4: *To perform a systematic review of the methodology used in analgesic trials in cancer pain, with focus on oral opioids*. Paper IV is a qualitative systematic review. In this paper, significant limitations in the methodology used in trials of oral opioids for cancer pain are identified. There is a need for standardised trial design and specific validity criteria for cancer pain. Concrete methodological recommendations for future trials are made.

6. Implications for clinical practice and future research

6.1 Trial methodology

Pain is difficult to study in the context of a randomised, controlled trial. This doctoral work pinpoints a need for uniform standards of reporting and more rigorous trial design, especially in analgesic studies in cancer pain. The poor quality of reporting and the methodological limitations of the research on opioids for cancer pain has been mentioned in previous reports[166 164], but does not seem to have resulted in any significant discussion or change in strategy. Considering the difficulties of research in this patient population, efforts to standardise trial design and reporting are needed. Whilst one trial design for all opioid trials in cancer pain is not feasible, a set of trial designs could be useful. Such a document is beyond the scope of this thesis, but could conceivably result from a consensus meeting between palliative care clinicians, pain researchers and statisticians having an interest in evidence-based pain relief. Such a consensus meeting which could be be comparable with the initiatives of the IMMPACT recommendations for chronic pain trials[111 112] is proposed in Paper IV.

6.2 Perioperative ketamine for acute postoperative pain

Clinical practice

Acute pain usually responds well to drug treatment (opioids), but opioid-related adverse effects are well documented and may contribute to increased in-hospital morbidity and costs. The rational for using perioperative ketamine should primarily be to reduce the total

perioperative opioid dose in patients undergoing specific surgical procedures where large doses of opioids are traditionally required. It may also be useful in opioid-tolerant surgical patient groups, such as drug abusers and cancer pain patients. Although there is no data to support the hypothesis, another rational for using ketamine would be in association with especially painful procedures involving nerve damage, with the aim of reducing hyperalgesia and possibly inhibiting or reducing the development of chronic postoperative pain. This type of treatment should be performed in the context of a clinical audit.

Future research

Since the spinal administration of ketamine is associated with unclear toxicity issues[70], future research on perioperative ketamine should focus on the common practice of intravenous administration, and on the question of optimal dose, and duration of treatment.

The interesting question is whether perioperative ketamine hastens recovery, reduces morbidity and reduces the development of chronic postoperative pain. Whether there is a clinical benefit of the demonstrated opioid-sparing effect of perioperative ketamine needs to be investigated. Clinically meaningful trial outcomes include measures of postoperative recovery. Opioid-related adverse effects should be carefully assessed and reported. Adverse effects should be reported as dichotomous data, and include a description of the method of assessment.

Studies in surgical patient groups where opioid-sparing is of particular importance, for example, cancer patients on high opioid doses, would be of interest. Studies with long-term follow-up in patients undergoing procedures known to be associated with persistent

postoperative pain, such as thoracotomy, are also indicated. Whether the isomers have advantages over the racemate is another relevant area for investigation.

6.3 Ketamine as an adjuvant to opioid for cancer pain

Clinical practice

Although the evidence is limited and does not permit recommendations for practice, this does not mean that the treatment does not work, or that clinicians should cease to treat refractory neuropathic cancer pain with low-dose ketamine. It simply means we currently lack reliable data. Findings from both Cochrane reviews support clinical observations that the morphine-sparing effect and the adverse effects of ketamine are dose-dependent, with low doses giving morphine-sparing and high doses producing adverse effects. The true clinical potential of ketamine for pain treatment in the palliative care patient population may lie in the use of low doses (for example 1 mg/kg/day as a subcutaneous infusion), adjuvant to opioid.

Future research

From the literature it is obvious that clinicians consider ketamine to be a useful drug in the treatment for refractory cancer pain. It is therefore important to document this treatment, and to learn more about the mechanisms of action, in order to optimalise the use of this drug. Randomised, controlled trials investigating the common practice of subcutaneous ketamine as adjuvant to opioid are needed. The use of oral ketamine should be documented initially in clinical audits, and if the treatment proves promising, be investigated in randomised, controlled trials. The peripheral effects of topical ketamine e.g. in the treatment of painful mucositis or pressure sores, is another area for investigation. Breakthrough or incident pain

is a common clinical problem and difficult to treat with analgesics. Ketamine in a rapid-acting formulation may prove useful in this context. The single published RCT on intranasal ketamine for breakthrough pain was performed on a mixed patient group, predominantly patients with chronic, non-cancer pain. Trials of longer duration in cancer pain patients are needed.

The Cochrane review on ketamine as an adjuvant to opioid for cancer pain (paper III) will be updated in the course of 2006. A preliminary search of PubMed in March 2006 indicated that RCT's are still lacking. As a direct result of this doctoral thesis, two trials have been designed. A randomised, double-blind placebo-controlled crossover study will investigate subcutaneous ketamine as adjuvant to morphine for refractory cancer pain. The second trial will investigate the peripheral effect of ketamine for painful mucositis in cancer patients. This is a randomised placebo-controlled crossover study comparing ketamine and morphine mouthwashes, and placebo.

Considering the postulated role of the NMDA receptor in opioid tolerance, together with the pre-clinical data reporting that low plasma concentrations of alfentanil increase the distribution of ketamine into the brain[66], further studies investigating the opioid/ ketamine relationship are warranted. The pharmacokinetics of ketamine as adjuvant to morphine are of primary interest since combining these drugs is common clinical practice.

References

1. Moore A, Edwards J, Barden J, McQuay H. *Bandolier's Little Book of Pain*. Oxford: Oxford University Press, 2003.

2. Weisenberg M, Raz T, Hener T. The influence of film-induced mood on pain perception. *Pain* 1998;76(3):365-375.

3. Montoya P, Larbig W, Braun C, Preissl H, Birbaumer N. Influence of social support and emotional context on pain processing and magnetic brain responses in fibromyalgia. *Arthritis Rheum* 2004;50(12):4035-4044.

4. Phillips ML, Gregory LJ, Cullen S, Coen S, Ng V, Andrew C, et al. The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. *Brain* 2003;126(Pt3):669-684.

5. Keefe FJ, Lumley M, Anderson T, Lynch T, Carson KL. Pain and emotion: new research directions. *J Clin Psychol* 2001;57(4):587-607.

6. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science* 2000;288(5472):1765-1768.

7. Beaulieu P, Rice ASC. Applied physiology of nociception. In: Rowbotham D, Macintyre P, editors. *Clinical Pain Management. Acute Pain*. London: Arnold, 2003.

8. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute Pain Management: Scientific Evidence, Second edition, 2005:10-12.

9. Dickenson AH. The pharmacology of excitatory and inhibitory amino acid-mediated events in the transmission and modulation of pain in the spinal cord. *Gen Pharmacol* 1997;28(5):633-638.

10. Tsai G, Coyle JT. Glutamatergic mechanisms in schizophrenia. *Ann Rev Pharmacol Toxicol* 2002;42:165-179.

11. Liu H, Wang H, Sheng M, Jan L, Jan YN, Basbaum AI. Evidence for presynaptic N-methyl-D-aspartate autoreceptors in the spinal cord dorsal horn. *Proc Natl Acad Sci USA* 1994;91:8383-8387.

12. Lipton SA. Paradigm shift in neuroprotection by NMDA receptor blockade: memantine and beyond. *Nat Rev* 2006;5:160-170.

13. Loftis JM, Janowsky A. The N-methyl-D aspartate receptor subunit NR2B: localization, functional properties, regulation , and clinical implications. *Pharmacol Ther* 2003;97:55-85.

14. Marcoux FW, Goodrich JE, Dominick MA. Ketamine prevents ischemic neuronal injury. *Brain Res* 1988;14(1-2):329-335.

15. Naslund TC, Hollier LH, Money SR, Facundus EC, Skenderis BS. Protecting the ischemic spinal cord during aortic clamping. The influence of anesthetics and hypothermia. *Ann Surg* 1992;215(5):409-415.

16. Himmelseher S, Pfenninger E, Giorgieff M. The effects of ketamine-isomers on neuronal injury and regeneration in rat hippocampal neurons. *Anesth Analg* 1996;83 (3):505-512.

17. Du J, Zhou S, Coggeshall RE, Carlton SM. N-methyl-D-aspartate-induced excitation and sensitization of normal and inflamed nociceptors. *Neuroscience* 2003;118(2):547-562.

18. Carlton SM, Coggeshall RE. Inflammation-induced changes in peripheral glutamate receptor populations. *Brain Res* 1999;820(1-2):63-70.

19. Petrie RX, Reid IC, Stewart CA. The N-methyl-D-aspartate receptor, synaptic plasticity, and depressive disorder. A critical review. *Pharmacol Ther* 2000;87(1):11-25.

20. Holtzheimer PE 3rd, Nemeroff CB. Advances in the treatment of depression. *NeuroRx* 2006;3(1):42-56.

21. Correll GE, Futter GE. Two case studies of patients with major depressive disorder given low-dose (subanesthetic) ketamine infusions. *Pain Med* 2006;7(1):92-95.

22. Stein C, Schafer M, Machelska H. Attacking pain at its source: new perspectives on opioids. *Nat Med* 2003;9(8):1003-1008.

23. Law PY, Wong YH, Loh HH. Molecular mechanisms and regulation of opioid receptor signaling. *Annu Rev Pharmacol Toxicol* 2000;40:389-430.

24. Trujillo KA, Akil H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. *Science* 1991;251(4989):85-87.

25. Tiseo PJ, Inturrisi CE. Attenuation and reversal of morphine tolerance by the competitive N-methyl-D-aspartate receptor antagonist, LY274614. *J Pharmacol Exp Ther* 1993;264(3):1090-1096.

26. Mao J, Price DD, Mayer DJ. Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C. *J Neurosci* 1994;14(4):2301-2312.

27. Simonin F, Schmitt M, Laulin JP, Laboureyras E, Jhamandas JH, MacTavish D, Matifas A, Mollereau C, Laurent P, Parmentier M, Kieffer BL, Bourguignon JJ, Simonet G. RF9, a potent and selective neuropeptide FF receptor antagonist, prevents opioid-induced tolerance associated with hyperalgesia. *Proc Natl Acad Sci USA* 2006;103(2):466-471.

28. Celerier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, Simonnet G. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. *Anesthesiology* 2000;92(2):465-472.

29. Gardell LR, King T, Ossipov MH, Rice KC, Lai J, Vanderah TW, Porreca F. Opioid receptor-mediated hyperalgesia and antinociceptive tolerance induced by sustained opiate delivery. *Neurosci Lett* 2006;396(1):44-49.

30. Porreca F, Ossipov MH, Gebhart GF. Chronic pain and medullary descending facilitation. *Trends Neurosci* 2002;25(6):319-325.

31. Zhang L, Zhang Y, Zhao Z-Q. Anterior cingulate cortex contributes to the descending facilitatory modulation of pain via dorsal reticular nucleus. *Eur J Neurosci* 2005;22(5):1141-1148.

32. Merskey H, Bogduk N, editors. *Classification of Chronic Pain, IASP Task Force on Taxonomy*. Second ed. Seattle: IASP Press, 1994.

33. Ready LB, Edwards WT. *Management of acute pain: A practical guide. Taskforce on acute pain.* Seattle: IASP Publications, 1992.

34. Tasmuth T, von Smitten K, Hietanen P, Kataja M, Kalso E. Pain and other symptoms after different treatment modalities of breast cancer. *Ann Oncol* 1995;6(5):453-459.

35. Kalso E, Mennander S, Tasmuth T, Nilsson E. Chronic post-sternotomy pain. *Acta Anaesthesiol Scand* 2001;45(8):935-939.

36. Cunningham J, Temple W, Mitchell P, Nixon J, Preshaw R, Hagen N. Cooperative hernia study. Pain in the postrepair patient. *Ann Surg* 1996;224(5):598-602.

37. Bisgaard T, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy: a prospective follow-up analysis. Scand J Gastroenterol 2005;40(11):1358-1364

38. Reuben S, Makari-Judson G, Lurie S. Evaluation of efficacy of the perioperative administration of venlafaxine XR in the prevention of postmastectomy pain syndrome. *J Pain Symptom Manage* 2004;27(2):133-139.

39. Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina SA, Shagin D, Max MB, Makarov SS, Maixner W. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005;14(1):135-143.

40. Rosseland L, Stubhaug A. Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. *Pain* 2004;112(3):248-253.

41. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med* 2006;144(2):127-134.

42. Keefe FJ, Abernethy AP, Campbell CL. Psychological approaches to understanding and treating disease-related pain. *Annu Rev Psychol* 2005;56:601-30.

43. Banning A, Sjøgren P, Henriksen H. Treatment outcome in a multidisciplinary cancer pain clinic. *Pain* 1991;47(2):129-134.

44. Mantyh PW, Clohisy DR, Kolzenburg M, Hunt SP. Molecular mechanisms of cancer pain. *Nat Rev Cancer* 2002;2(3):201-209.

45. Cancer, pain relief and palliative care. Geneva: World Health Organization. WHO Technical Report Series No 408, 1990.

46. Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical centre. *Pain* 2003;101(1-2):55-64.

47. Svendsen KB, Andersen S, Arnason S, Arner S, Breivik H, Heiskanen T, Kalso E, Kongsgaard UE, Sjogren P, Strang P, Bach FW, Jensen TS. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. *Eur J Pain* 2005;9(2):195-206.

48. Maurset A, Skoglund LA, Øye ILS. The analgetic action of ketamine in humans is non-opioid and mediated by PCP-receptors. In: Domino EF KJ-M, editor. *Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology*. Ann Arbor: NPP Books, 1988:541-544.

49. Øye I, Hustveit O, Maurset A, Moberg ER, Paulsen O, Skoglund LA. The chiral forms of ketamine as probes for NMDA receptor functions in humans. In: Kameyama T NT, Domino EF, eds. *NMDA Receptor Related Agents, Biochemistry, Pharmacology and Behaviour*. Ann Arbor: NPP Books, 1991:381-389.

50. Maurset A, Skoglund LA, Øye I. Comparison of ketamine and pethidine in experimental and postoperative pain. *Pain* 1989;36(1):37-41.

51. Mikkelsen S, Ilkjaer J, Brennum J, Borgbjerg FM, Dahl JB. The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans. *Anesthesiology* 1999;90(6):1539-1545.

52. Eide PK JE, Stubhaug A, Bremnes J, Breivik H. Relief of postherpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994;58(3):347-354.

53. Laulin JP, Maurette P, Corcuff JB, Rivat C, Chauvin M, Simonnet G. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. *Anesth Analg* 2002;94(5):1263-1269.

54. Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM. Norketamine, the main metabolite of ketamine , is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *Eur J Pharmacol* 1997;333(1):99-104.

55. Arendt-Nielsen L, Nielsen J, Petersen-Felix S, Schnider TW, Zbinden AM. Effect of racemic mixture and the S (+) isomer of ketamine on temporal and spatial summation of pain. *Br J Anaesth* 1996;77(5):625-631.

56. Hartvig P, Valtysson J, Lindner KJ, Kristensen J, Karlsen R, Gustafsson LL, Persson J, Svensson JO, Oye I, Antoni G, et al. Central nervous system effects of subdissociative doses of (S)- ketamine are related to plasma and brain concentrations measured with positron emission tomography in healthy volunteers. *Clin Pharmacol Ther* 1995;58(2):165-173.

57. Grahame Smith D, Aronson J. *Oxford Textbook of Clinical Pharmacology and Drug Therapy*. Third ed. Oxford: Oxford University Press, 2002.

58. Lahtinen P, Kokki H, Hakala T, Hynynen M. S(+)-ketamine as an analgesic adjunct reduces opioid consumption after cardiac surgery. *Anesth Analg* 2004;99(5):1295-1301.

59. Shimoyama M, Shimoyama N, Gorman A, Elliott K, Inturissi C. Oral ketamine is antinociceptive in the rat formalin test: role of the metabolite, norketamine. *Pain* 1999;81(1-2):85-93.

60. Kharasch ED, Labroo R. Metabolism of ketamine stereoisomers by human liver microsomes. *Anesthesiology* 1992;77(6):1201-1207.

61. Ihmsen H, Geisslinger G, Schuttler J. Stereoselective pharmacokinetics of ketamine: R(-) ketamine inhibits the elimination of S(+) ketamine. *Clin Pharmacol Ther* 2001;70(5):431-438.

62. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. *Br J Anaesth* 1981;53(8):805-810.

63. Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management: Preclinical animal studies, recent clinical experience and future research directions. *J Pain Symptom Manage* 2000;20(5):358-373.

64. Clements JA, Nimmo WS, Grant IS. Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. *J Pharm Sci* 1982;71(5):539-542.

65. Carr DB, Goudas LC, Denman WT, Brookhoff D, Staats PS, Brennen L, Green G, Albin R, Hamilton D, Rogers MC, et al. Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study. *Pain* 2004;108(1-2):17-27.

66. Edwards SR, Minto CF, Mather LE. Concurrent ketamine and alfentanil administration: pharmacokinetic considerations. *Br J Anaesth* 2002;88(1):94-100.

67. White PF, Way WL, Trevor AJ. Ketamine - its pharmacology and therapeutic uses. *Anesthesiology* 1982;56(2):119-136.

68. Olney JW, Wozniak DF, Jevtovic-Todorovic V, Farber NB, Bittigau P, Ikonomidou C. Drug-induced apoptotic neurodegeneration in the developing brain. *Brain Pathology* 2002;12(4):488-498.

69. Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Wang H, Labruyere J, et al. Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. *Br J Pharmacol* 2005;146(2):189-197.

70. Eisenach J, Yaksh T. Epidural ketamine in healthy children-What's the point? *Anesth Analg* 2003;96(2):626-633.

71. Malinovsky JM, Lepage JY, Cozian A, Mussini JM, Pinaudt M, Souron R. Is ketamine or its preservative responsible for neurotoxicity in rabbit? *Anesthesiology* 1993;78(1):109-115.

72. Karpinski N, Dunn J, Hansen L, Masliah B. Subpial vacuolar myelopathy after intrathecal ketamine: report of a case. *Pain* 1997;73(1):103-105.

73. Stotz M, Oehen HP, Gerber H. Histological findings after long-term infusion of intrathecal ketamine for chronic pain: a case report. *J Pain Symptom Manage* 1999;18(3):223-228.

74. Vranken JH, Troost D, Wegener JT, Kruis MR, van der Vegt MH. Neuropathological findings after continuous intrathecal administration of S(+)-ketamine for the management of neuropathic cancer pain. *Pain* 2005;117(1-2):231-235.

75. Degenhardt L, Copeland J, Dillon P. Recent trends in the use of "club drugs": an Australian review. *Subst Use Misuse* 2005;40(9-10):1241-1256.

76. Freese TE, Miotto K, Reback CJ. The effects and consequences of selected club drugs. *J Subst Abuse Treat* 2002;23(2):151-156.

77. Curran HV, Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. *Addiction* 2001;96(5):749-760.

78. Narendran R, Frankle WG, Keefe R, Gil R, Martinez D, Slifstein M, Kegeles LS, Talbot PS, Huang Y, Khenissi L et al. Altered prefrontal dopaminergic function in chronic, recreational ketamine users. *Am J Psychiatry* 2005;162(12):2352-2359.

79. Beardsley PM, Balster RL. Behavioral dependence on phencyclidine and ketamine in the rat. *J Pharmacol Exp Ther* 1987;242(1):203-211.

80. Maxwell JC. Party drugs: properties, prevalence, patterns and problems. *Subst Use Misuse* 2005;40(9-10):1203-1240.

81. Bell RF, Kalso E. Is intranasal ketamine an appropriate treatment for chronic non-cancer breakthrough pain? *Pain* 2004;108(1-2):1-2.

82. Lipton SA. NMDA receptors, glial cells, and clinical medicine. *Neuron* 2006;50(1):9-11.

83. Duedahl TH, Romsing J, Moiniche S, Dahl JB. A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. *Acta Anaesthesiol Scand* 2006;50(1):1-13.

84. The use of drugs beyond licence in palliative care and pain management: The Association for Palliative Medicine and the British Pain Society, 2005:5.

85. Cochrane AL. Effectiveness and Efficiency. Random Reflections on Health Services. London: Nuffield Provincial Hospitals Trust, 1972.

86. Cochrane AL. 1931-1971: a critical review, with particular reference to the medical profession. *Medicines for the year 2000*. London: Office of Health Economics, 1979:1-11.

87. Starr M, Chalmers I. The evolution of the Cochrane Library, 1988-2003: Update software:Oxford.

88. L'Abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Ann Intern Med* 1987;107(2):224-233.

89. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Eng J Med* 1988;318(26):1728-1733.

90. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;310(6977):452-454.

91. Jadad AR, McQuay HJ. Meta-analyses to evaluate analgesic interventions: a systematic qualitative review of their methodology. *J Clin Epidemiol* 1996;49(2):235-243.

92. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup D. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999;354(9193)1896-1900.

93. Terrin N, Schmid C, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *J Clin Epidemiol* 2005;58(9):894-901.

94. Moher D, Tsertsvadze A. Systematic reviews: when is an update an update. *Lancet* 2006;367(9514):881-883.

95. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991;44(11):1271-1278.

96. Moore RA. Techniques of systematic review:qualitative versus quantitative. In: Tramer M, editor. *Evidence Based Resource in Anaesthesia and Analgesia*. London: BMJ Books, 2000:67-84.

97. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273(5):408-412.

98. Kalso E, Moore RA. Five easy pieces on evidence- based medicine (2). *Eur J Pain* 2000;4(3):321-324.

99. Beecher HK. The powerful placebo. *JAMA* 1955;159(17):1602-1606.

100. McQuay H, Carroll D, Moore A. Variation in the placebo effect in randomised controlled trials of analgesics: all is as blind as it seems. *Pain* 1996;64(2):331-335.

101. Moore RA, Gavaghan DJ, Tramer MR, Collins SL, McQuay HJ. Size is everything-large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;78(3):217-220.

102. Moore RA, Tramer MR ,Carroll D, Wiffen PJ, McQuay HJ. Quantitative systematic review of topically-applied non-steroidal anti-inflammatory drugs. *BMJ* 1998;316(7128):333-338.

103. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ.. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1-12.

104. Smith LA, Oldman AD, McQuay HJ, Moore RA. Teasing apart quality and validity in systematic reviews: an example from acupuncture trials in chronic neck and back pain. *Pain* 2000;86(1-2):119-32.

105. McQuay H, Moore A. *An Evidence-based Resource for Pain Relief*. Oxford: Oxford University Press, 1998.

106. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardsen WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312(7023):71-72.

107. Jackson K, Ashby M, Goodchild C. Subanesthetic ketamine for cancer pain: by insisting on level I/II evidence, do we risk throwing the baby out with the bathwater? *J Pain Symptom Manage* 2005;29(4):328-330.

108. Bandolier: http://www.jr2.ox.ac.uk/Bandolier/

109. Oxford Pain Site: http://www.jr2.ox.ac.uk/Bandolier/booth/painpag/index2.html

110. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olken I, Pitkin R, Rennie D, Schulz KF, Simel D, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;276(8):637-639.

111. Turk D, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003;106(3):337-345.

112. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113(1-2):9-19.

113. Collins SL, Edwards J, Moore RA, Smith LA, McQuay HJ. Seeking a simple measure of analgesia for mega-trials: is a single global assessment good enough? Pain 2001;91(1-2):189-194.

114. Stubhaug A, Breivik H. Post-operative analgesic trials: some important issues. In: Breivik H, editor. Bailliere's Clinical Anesthesiology. London: Bailliere Tindall, 1995:555-589.

115. Kalso E, Smith LA, McQuay H, Moore RA. No pain, no gain: clinical excellence and scientific rigour- lessons learned from IA morphine. Pain 2002;98(3):269-275.

116. Breivik EK, Bjornsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. Clin J Pain 2000;16(1):22-28.

117. Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. J Pain Symptom Manage 1999;18(6):427-437.

118. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-571.

119. McNair DM, Lorr M, Droppleman LF. Profile of Mood States. San Diego, CA: Educational and Industrial Testing Service, 1971.

120. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000;93(4):1123-1233.

121. Woolf CJ, Chong MS. Preemptive analgesia- treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77(2):362-379.

122. Dahl JB, Mathiesen O, Moiniche S. 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. Acta Anaesthesiolog Scand 2004;48(9):1130-1136.

123. Dahl JB, Moiniche S. Pre-emptive analgesia. Br Med Bulletin 2004;71:13-27.

124. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. BMJ 1996;313(7048):36-39.

125. Piaggio G, Elbourne D, Altman DG, Pocock S, Evans S. Reporting of noninferiority trials and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006;295(10):1152-1160.

126. World Medical Association.World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, 1964 (amended 1975,1983,1989,1996, 2000, 2002, 2004) (http://www.wma.net/e/policy/b3.htm)

127. Clarke M, Oxman A, editors. Cochrane Reviewer's Handbook. Issue 4 ed. Oxford: The Cochrane Collaboration, 2001.

128. Tasmuth T, Kataja M, Blomquist C, von Smitten K, Kalso E. Treatment-related factors predisposing to chronic pain in patients with breast cancer- a multivariate approach. Acta Oncol 1997;36(6):625-630.

129. Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996;12(1):50-55.

130. Romundstad L, Breivik H, Roald H, Skolleborg K, Romundstad PR, Stubhaug A. Chronic pain and sensory changes after augmentation mammoplasty. Long term effects of preincisional administration of methylprednisolone. Pain 2006;In press.

131. Obata H, Saito S, Fujita N, Fuse Y, Ishizaki K, Goto F. Epidural block with mepivacaine before surgery reduces long-term post-thoracotomy pain. Can J Anaesth 1999;46(12):1127-1132.

132. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief- the role of timing of analgesia. Anesthesiology 2002;96(3):725-741.

133. Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, Kincaid JC, Ochoa JL, Pary GJ, Weimer LH, et al. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2003;60(6):898-904.

134. Kolesnikov YA, Pasternak GW. Peripheral blockade of topical morphine tolerance by ketamine. Eur J Pharmacol 1999;374(2):R1-2.

135. Warncke T, Jørum E, Stubhaug A. Local treatment with the N-methyl-D-aspartate receptor antagonist ketamine, inhibit development of secondary hyperalgesia in man by a peripheral action. Neurosci Lett 1997;227(1):1-4.

136. Tverskoy M, Oren M, Vaskovich M, Dashkovsky I, Kissin I. Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: a study in postoperative patients. Neurosci Lett 1996;215(1):5-8.

137. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Anesthesiology 2005;103(1):140-146.

138. Labuz D, Berger S, Mousa SA, Zollner C, Rittner HL, Shaqura MA, Segovia-Silvestre T, Przewlocka B, Stein C, Machelska H. Peripheral antinociceptive effects of exogeneous and immune cell-derived endomorphins in prolonged inflammatory pain. J Neurosci 2006;26(16):4350-4358.

139. Wenk HN, Brederson JD, Honda CN. Morphine directly inhibits nociceptors in inflamed skin. J Neurophysiol 2006;95(4):2083-2097.

140. Modalen AO, Quiding H, Frey J, Westman L, Lindahl S. A novel molecule with peripheral opioid properties: the effects on hypercarbicand hypoxic ventilation at steady-state compared with morphine and placebo. Anesth Analg 2006;102(1):104-109.

141. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg 2004;99(2):482-495.

142. Elia N, Tramer MR. Ketamine and postoperative pain- a quantitative systematic review of randomised trials. Pain 2005;113(1-2):61-70.

143. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain 1999;82(2):111-125.

144. McCartney CJ, Sinha A, Katz J. A qualitative systematic review of the role of N-methyl-D- aspartate receptor antagonists in preventive analgesia. Anesth Analg 2004;98(5):1385-1400.

145. De Kock M, Lavand'homme P, Waterloos H. 'Balanced analgesia' in the perioperative period: is there a place for ketamine? Pain 2001;92(3):373-380.

146. Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, Chauvin M. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005;103(1):147-155.

147. Sen S, Ozmert G, Aydin ON, Baran N, Caliskan E. The persisting analgesic effect of low-dose intravenous ketamine after spinal anaesthesia for caesarean section. Eur J Anaesthesiol 2005;22(7):518-523.

148. Ganne O, Abisseror M, Menault P, Malhiere S, Chambost V, Charpiat B, Ganne C, Viale JP. Low-dose ketamine failed to spare morphine after a remifentanil-based anesthesia for ear, nose and throat surgery. Eur J Anaesthesiol 2005;22(6):426-430.

149. Bilgin H, Ozcan B, Bilgin T, Kerimoglu B, Uckunkaya N, Toker A, Alev T, Osma S. The influence of timing of systemic ketamine administration on postoperative morphine consumption. J Clin Anesth 2005;17(8):592-597.

150. Dahl J, Kehlet H. Postoperative pain and its management. In: McMahon S, Koltzenburg M, editors. Wall and Melzack's Textbook of Pain, Fifth ed.Churchill Livingstone, 2005:638.

151. Lussier D, Portenoy R. Adjuvant analgesics in pain management. In: Doyle D, Hanks G, Cherny N, Calman K, editors. Oxford Textbook of Palliative Medicine. Third ed. Oxford: Oxford University Press, 2004:361.

152. Mitchell AC. Generalized hyperalgesia and allodynia following abrupt cessation of subcutaneous ketamine infusion. Palliat Med 1999;13(5):427-428.

153. Oshima E, Tei K, Kayazawa H, Urabe N. Continuous subcutaneous injection of ketamine for cancer pain. Can J Anaesth 1990;37(3):385-386.

154. Lloyd-Williams M. Ketamine for cancer pain. J Pain Symptom Manage 2000;19(2):79-80.

155. Lossignol DA, Obiols-Portis M, Body JJ. Successful use of ketamine or intractable cancer pain. Support Care Cancer 2005;13(3):188-193.

156. Akin Takmaz S, Inan N, Gunal S, Kaymak C, Sakalli M, Dikmen B. Ketamine combined with morphine for the management of cancer pain in a patient with meperidine tolerance and addiction. Agri 2005;17(3):44-47.

157. Mercadante S, Acuri E, Ferrara P, Villari P, Mangione S. Alternative treatments of breakthrough pain in patients receiving spinal analgesics for cancer pain. J Pain Symptom Manage 2005;30(5):485-491.

158. Fitzgibbon EJ, Viola R. Parenteral ketamine as an analgesic adjuvant for severe pain: development and retrospective audit of a protocol for a palliative care unit. J Palliat Med 2005;8(1):49-57

159. Bell RF, Kalso E. Subanesthetic ketamine for cancer pain and scientific rigor in cancer pain trials. A reply to Jackson et al. J Pain Symptom Manage 2006;31(5):386.

160. Kannan TR, Saxena A, Bhatnagar S, Barry A. Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. J Pain Symptom Manage 2002;23(1):60-65.

161. Haines DR, Gaines SP. N of 1 randomised controlled trials of oral ketamine in patients with chronic pain. Pain 1999;83(2):283-287.

162. Mikkelsen S, Jorgensen H, Larsen PS, Brennum J, Dahl JB. Effect of oral ketamine on secondary hyperalgesia, thermal and mechanical pain thresholds, and sedation in humans. Reg Anesth Pain Med 2000;25(5):452-458.

163. Quigley C. Hydromorphone for acute and chronic pain. Cochrane Database Syst Rev 2002(1):CD003447.

164. Wiffen PJ, Edwards JE, Barden J, McQuay HJ. Oral morphine for cancer pain. Cochrane Database Syst Rev 2003(4):CD003868.

165. Reid CM, Martin RM, Sterne JA, Davies AN, Hanks GW. Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. Arch Intern Med 2006;166(8):837-843.

166. Goudas L, Carr DB, Bloch R, Balk E, Ioannidis JP, Terrin N, Gialeli-Goudas M, Chew P, Lau J. Management of cancer pain. Evidence Report / Technology Assessment No. 35: AHRQ Publication No. 02-E002. Rockville, MD: Agency for Healthcare Research and Quality, 2001.

167. Kongsgaard UE, Kaasa S, Dale O, Ottesen S, Nordøy T, Hessling SE, von Hofacker S, Bruland ØS. Lindring av smerter hos kreftpasienter. Oslo: Norwegian Knowledge Centre for the Health Services, 2005:158.

168. Caraceni A, Brunelli C, Martini C, Zecca E, De Conno F. Cancer pain assessment in clinical trials. A review of the literature (1999-2002). J Pain Symptom Manage 2005;29(5):507-519.

169. Hoskin PJ, Poulain P, Hanks GW. Controlled-release morphine in cancer pain. Is a loading dose required when the formulation is changed? Anaesthesia 1989;44(11):897-901.

170. Broomhead A, Kerr R, Tester W, O'Meara P, Maccarrone C, Bowles R, Hodsman P. Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. J Pain Symptom Manage 1997;14(2):63-73.

171. Houde RW, Wallenstein SL, Rogers A. Clinical pharmacology of analgesics: 1. A method of assaying analgesic effect. Clin Pharmacol Ther 1960;1(2):163-174.

172. Stambaugh JE Jr. Additive analgesia of oral butorphanol/ acetaminophen in patients with pain due to metastatic carcinoma. Curr Ther Res 1982;31(3):386-392.

173. Stambaugh JE Jr, Lane C. Analgesic efficacy and pharmacokinetic evaluation of meperidine and hydroxyzine, alone and in combination. Cancer Invest 1983;1(2):111-117.

174. Stambaugh JE Jr, McAdams J. Comparison of intramuscular dezocine with butorphanol and placebo in chronic cancer pain: a method to evaluate analgesia after both single and repeated doses. Clin Pharmacol Ther 1987;42(2):210-219.

175. Stambaugh JE Jr, McAdams J. Comparison of the analgesic efficacy and safety of oral ciramadol, codeine and placebo in patients with chronic cancer pain. J Clin Pharmacol 1987;27(2):162-166.

176. Farrar JT, Cleary J, Rauck R, Busch MA, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. J Natl Cancer Inst 1998;90(8):611-616.